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SYNTHETIC ENTEROBACTIN ANALOGS. CARBOXAMIDO-2,3-DIHYDROXYTEREPHTHALATE CONJUGATES OF SPERMINE AND SPERMIDINE

Frederick L. Weitl, Kenneth N. Raymond, and Patricia W. Durbin

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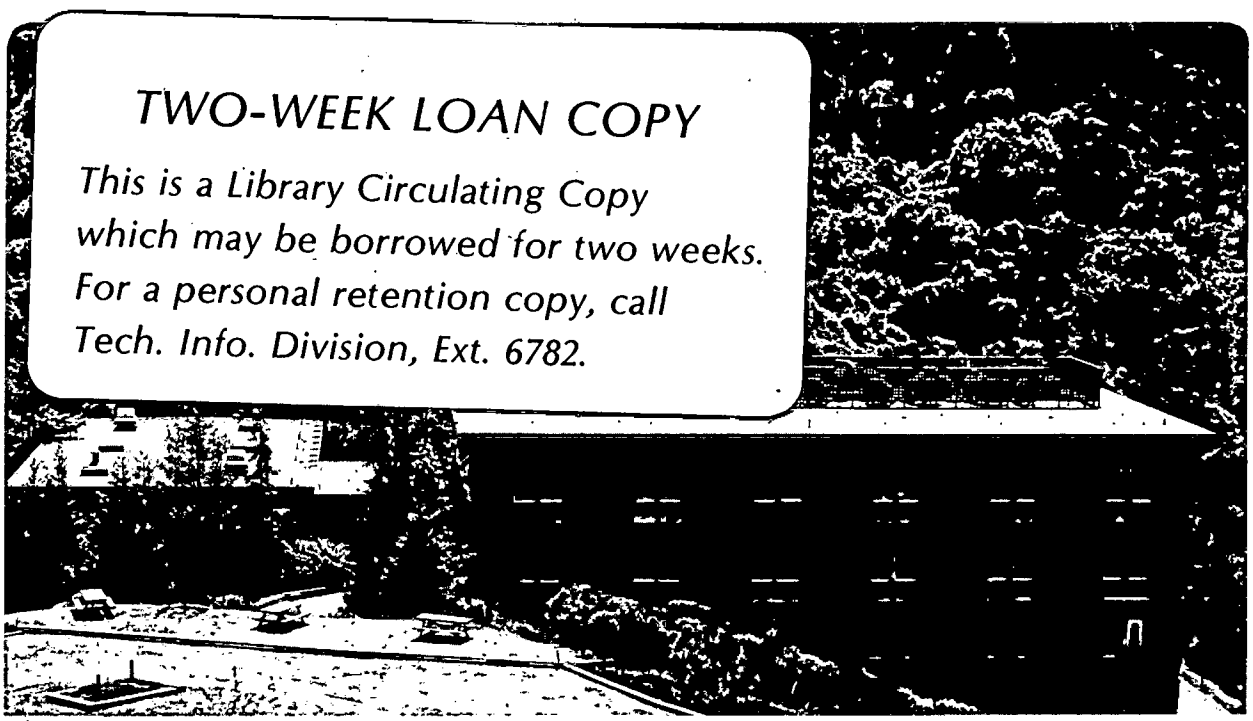

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Synthetic Enterobactin Analogs.[1] Carboxamido-2,3-Dihydroxyterephthalate Conjugates of Spermine and Spermidine

By

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Contribution from Divisions of Materials and Molecular Research and Biology and Medicine, Lawrence Berkeley Laboratory; and Department of Chemistry; University of California, Berkeley, California 94720

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Abstract

Two examples of a new class of synthetic polycatecholate ligands, the carboxamido-2,3-dihydroxyterephthalate conjugates of spermine (8) and of spermidine (10) have been synthesized via the generally useful synthon, methyl-2,3-dimethoxyterephthaloyl chloride (6). Initial biological evaluation reveals tetrameric terephthalate (8) to be an extremely effective agent for sequestering and removing plutonium from mice; a single 25 μmol per kg. (i.p.) dose of (8) removed 73% of the plutonium citrate previously injected (iv., 1 hr earlier). Under the same conditions, trimeric terephthalate (10) excreted only 49% of injected plutonium. *In vitro* kinetic experiments have shown (10) rapidly and quantitatively removed Fe from human transferrin. These results are discussed in relation to the design of metal-ion specific sequestering agents.

Introduction

We have previously described two related research programs for the design and synthesis of specific sequestering agents for iron(III)[3,4] and actinide(IV) metal ions.[4-8] In the case of iron, since the body lacks any mechanism for removing excess amounts of this essential element, it can be an acute or chronic poison. A major program is underway for the development of iron chelating agents to be used in treating Cooley's anemia, a genetic disease which results in chronic iron overload.[9] Our ferric-ion chelating agents are modeled after the siderophores, a class of low-molecular-weight iron sequestering and transport agents that are produced by microbes. The most powerful natural iron chelator known is enterobactin.[10] Since this siderophore incorporates catechol chelating agents (in the form of 2,3-dihydroxybenzoyl groups, DHB), our initial approach has been the incoporation of several substituted DHB groups into multidentate chelate molecules.

Of the radioactive isotopes produced as by-products of the nuclear fuel cycle, the major long-term radiation hazard is posed by the transuranium actinides. Of the actinides, plutonium is a particularly dangerous biological hazard because of the chemical and biological similarities of Pu(IV) and Fe(III).[11-14] Incorporated plutonium is bound by transferrin, the mammalian iron transport protein, at the same site that normally binds Fe(III) and is then concentrated in iron storage sites, where most of it remains indefinitely. In order to prepare specific sequestering agents for Pu(IV) and other actinide ions, we have explicitly recognized this similarity of Pu(IV) and Fe(III) in using as chemical models the microbial chelating agents which are so specific for Fe(III).

As direct analogs of the siderophores such as enterobactin[10] and a threonine conjugate of spermidine isolated by Tait,[15] we have prepared tetrameric[5] and trimeric[16] 2,3-dihydroxybenzoyl conjugates incorporating certain linear, cyclic, and platform amines. Direct sulfonation of these compounds produced the 5-sulfonato-2,3-dihydroxybenzamide analogues.[3,19] These are potent sequestering agents for plutonium *in vivo*[6] and iron *in vitro*.[18] The sulfonated derivatives show high water solubility at any pH, improved resistance toward oxidation and increased phenolic acidity; these properties make them better ligands under physiological conditions.

A most important property of any sequestering agent to be used in chelation therapy over long time periods is that it be orally active. Of the compounds tested to date, none of the effective sequestering agents for iron or the actinides have achieved this goal. Some promise was shown by the simple monomeric catechol derivative 2,3-dihydroxybenzoic acid, and it has undergone clinical tests in man.[19] The oral activity of this compound may be due to its dual acid-anion functionality. In addition, the ortho carboxylate group gives two possible modes of metal binding (catecholate or salicylate type) and these are pH dependent.[10]

Thus the introduction of the 4-carboylate group might be expected to substantially improve the usefulness of the catechol sequestering agents. We now report the synthesis of the title compounds. These are the first examples of 4-carboxylate-catechoyl amides. As before, the tetrameric catecholate (**8**) was designed to satisfy the eight-coordinate geometry of a single Pu(IV) ion (the predominant *in vivo* oxidation state[11])

through the four pairs of phenolic oxygens. The related trimer (10) is potentially a six-coordinate catecholate ligand for Fe(III).

General Procedure

To achieve good water solubility in the catecholate ligands via the carboxylate moiety, the symmetrical 2,3-dihydroxyterephthalic acid was chosen as monomeric unit. Thus the dry disodium salt of catechol (1) was carboxylated according to a modified procedure of Cason and Dyke.[20] The dry disodium carboxylate derivative (2) provided crystalline dimethyl ester (3) upon refluxing with HCl/CH_3OH. Permethylation to ligand (4) was achieved with K_2CO_3/dimethyl sulfate in refluxing acetone. When a hot CH_3OH solution of (4) was treated with 1 equiv. of 6 N NaOH overnight, a 70% yield of the monosodium salt (5) resulted. Neat $SOCl_2$ at 50°C converted this compound directly to acid chloride (6), the necessary synthon for preparation of permethyl tetraamide (7) and permethyl triamide (9). Demethylation with excess BBr_3 at room temperature provided the spermine (8) and spermidine (10) derivatives. Both were purified by acid-base precipitation and were dried over P_2O_5 under vacuum.

Experimental

Melting points were taken on a Buchi apparatus in open capillaries and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 283 instrument. Proton NMR spectra were recorded on a Varian A-60 instrument using Me_4Si or 3-(Me_3Si)-1-propane sulfonic acid, sodium salt, hydrate as internal standard. Evaporations were accomplished under

vacuum (oil pump) with a Buchi Rotovapor-RE at ≤ 55°C. Thin layer chromatography (TLC) was performed on precoated 60F -254 silica gel sheets, developed in tetrahydrofuran C_6H_{12}/H_2O (93:7:5) and visualized with UV, I_2 vapor, or Fe^{+3}/H_2O/EtOH spray. Column chromatography was performed using 60-200 mesh silica gel in a 35 x 2.5 cm o.d. column and fractions monitored by TLC. Microanalyses and mass spectra (m/e, 70 eV) were performed by Analytical Services, Chemistry Department, University of California, Berkeley. Both spermine (the amine component of 7 and 8) and spermidine (the amine component of 9 and 10) were purchased from the Ames Laboratories, Inc., Milford, Conn. The BBr_3 used was a product of Alfa Division, Ventron Corporation, Danvers, Mass. All chemical analyses were within 0.4% of calculated values. Those elements analyzed appear after each empirical formula.

Disodium 2,3-dihydroxyterephthalate (2). The procedure of Cason and Dyke[20] has been modified as follows: To catechol, 1 (33 g, 300 mmol) dissolved in 300 ml CH_3OH (under argon atmosphere) was added at once NaOH pellets (24 g, 600 mmol). The resulting solution was allowed to sit overnight then evaporated *in vacuo* (105°, 48 hr) to a light tan, dry powder which was further treated with excess CO_2 (1100 psi) at 175-200° (48 hr) in a static, stainless steel bomb. The light tan solid product was acidified with hot aq. 6N HCl, filtered, and washed with hot H_2O. The solid product was dissolved in hot aqueous NaOH, (pH 9), treated twice with charcoal, then cooled in an ice bath to obtain nearly white, crystalline (2) (17.6 g, 24%): mp > 300°; ^{1}HNMR (D_2O) δ 7.45 (s, 2H, ArH). The remaining (basic) solution was

acidified with aq. HCl, to obtain nearly white 2a (20.8 g, 35%): mp 289-90°;[20] ^{1}HNMR (DMSO) δ 7.42 (s, 2H ArH).

Anal. ($C_8H_4O_6Na_2$) Na.

Dimethyl-2,3-dihydroxyterephthalate (3). To a slurry of 2 (12.1 g, 58 mmol) in 150 ml CH_3OH was added excess HCl via gas diffusion tube. After 60 hr under reflux, the hot reaction mixture was filtered to remove NaCl. Ice bath cooling provided white needles of 3 (10.7 g, 82%): mp 141-3°;[21] ^{1}HNMR (DMSO) δ 4.13 (s, 6H, $-CO_2CH_3$), 7.36 (s, 2H, ArH).

Dimethyl-2,3-dimethoxyterephthalate (4). The following materials were combined and kept at reflux (under argon) 48 hr: 3 (13.6 g, 60 mmol), K_2CO_3 (16.6 g, 120 mmol), dimethyl sulfate (11.4 ml, 120 mmol), acetone (150 ml). Filtration while hot to remove salts, followed by distillation *in vacuo* gave 4 (10.3 g, 68%): $b_{0.5}$ 130°;[15] n_D^{22} 1.5156; ^{1}HNMR (CCl_4) δ 3.8-4.0 (two s, 12H, OCH_3 + CO_2CH_3), 7.49 (s, 2H, ArH).

Sodium Methyl 2,3-dimethoxyterephthalate (5). To 4 (10.1 g, 40 mmol) in CH_3OH (200 ml) solution was added NaOH (1.6 g, 40 mmol) and H_2O (5 ml). The resulting solution was refluxed overnight, then concentrated *in vacuo* to about 1/4 volume. Addition of acetone (several volumes) to precipitate a small amount of disodium by-product followed by filtration gave a clear colorless solution. Addition of ethyl ether (1-2 vol) with scratching gave white microcrystalline 5 (7.1 g, 68%) which was dried at 75° (< 1 mm): mp 205-7°; ^{1}HNMR (D_2O) δ 3.9-4.0 (two s, 9H, OCH_3 + CO_2CH_3), 7.30 (d, 1H, J_{AB} = 9 Hz, ArH), 7.70 (d, 1H, J_{AB} = 9 Hz, ArH).

Anal. ($C_{11}H_{11}O_6Na$) C, H, Na.

Methyl-2,3-dimethoxyterephthaloyl chloride (6). Compound 5 (6.5 g, 25 mmol) was added in portions to $SOCl_2$ (25 ml) with the evolution of SO_2 and heat. After stirring overnight under a Drierite tube an equal volume of CCl_4 was added and the mixture filtered to remove NaCl. Coevaporation of this solution *in vacuo* with CCl_4 (3 x 30 ml) gave white, crystalline CCl_4-soluble 6 (∿ 100%), which was satisfactory for immediate use in the synthesis of 7 and 9.

N,N',N",N"'-Tetra(2,3-dimethoxy-4-carbomethoxybenzoyl)-1,5,10,14-tetraazatetradecane (7). To crude, dry 6 (25 mmol) was added tetrahydrofuran (THF) (50 ml), spermine (1.2 g, 6.0 mmol), and NEt_3 (3.5 ml, 25 mmol). An immediate white precipitate formed and the evolution of heat was evident. The reaction was allowed to stir overnight at ambient temperature in a stoppered flask. Filtration, THF wash, then oven drying provided $NEt_3 \cdot HCl$ (3.2 g, 97%). Evaporation of the THF solution *in vacuo* gave a viscous oil; this was dissolved in a small amount of $CHCl_3$, then eluted from a silica gel column (initially with $CHCl_3$). The product was eluted with 2-4% CH_3OH in $CHCl_3$ (v/v): TLC, R_f 0.63. Coevaporation (*in vacuo*) with CCl_4 (3 x 50 ml) gave a glassy solid which when dried at 56°, 5 microns, 20 hr gave 7·2/3 CCl_4 (6.2 g, 86%): ir (neat, NaCl) 3380 (-CO<u>NH</u>-), 2940 (-CH-), 1730 (-<u>CO</u>$_2$CH$_3$), 1665-1625 (-<u>CO</u>NR-), 1520, 1455, 1400, 1305-1235, 1020, 755 cm^{-1}; ^{1}HNMR (CCl_4) δ 1.2-2.2 (broad m, 8H, NCH$_2$<u>CH$_2$</u>), 3.0-4.1 (broad m, 12H, N<u>CH$_2$</u>CH$_2$), 2.8-4.2 (broad s, 36H, -O<u>CH$_3$</u> + -CO$_2$<u>CH$_3$</u>), 6.8-7.9 (broad m, 8H, Ar<u>H</u>).

Anal. ($C_{54}H_{66}N_4O_{20} \cdot 2/3\ CCl_4$) C, H, N.

N,N',N"-Tris(2,3-dimethoxy-4-carbomethoxybenzoyl)-1,5,10-triazadecane (9). Using the same procedure as for 7, the following ingredients were combined: 6 (25 mmol), THF (50 ml), spermidine (1.2 g, 8 mmol), NEt_3 (3.5 ml, 25 mmol). This resulted, after purification as before, in CCl_4-soluble 9: TLC, R_f 0.71. Coevaporation (in vacuo) with CCl_4 (3x 50 ml) gave a glassy solid which when dried (56°, 5 microns, 20 hr) gave 9·1/2 CCl_4 (6.5 g, 92%): ir (neat, NaCl) 3380 (-CONH-), 2950 (-CH-), 1730 ($-CO_2CH_3$), 1665-1630 (-CONR-), 1525, 1455, 1400, 1300-1235, 1020, 755 cm^{-1}; ^{1}HNMR (CCl_4) δ 1.2-2.2 (broad m, 6H, $N-CH_2CH_2-$), 3.0-4.1 (broad m, 8H, $N-CH_2-$), 3.8-4.2 (broad s, 27H, $-OCH_3$ + $-CO_2CH_3$), 6.8-8.0 (broad m, 6H, ArH).

Anal. ($C_{40}H_{49}N_3O_{15}$·1/2 CCl_4) C, H, N.

N,N',N",N"'-Tetra(2,3-dihydroxy-4-carboxybenzoyl)-1,5,10,14-tetraazatetradecane (8). Precursor 7 (6.0 g, 5.5 mmol) dissolved in CCl_4 (75 ml) was added dropwise via addition funnel (under argon) to a CH_2Cl_2 (175 ml) solution of BBr_3 (7 mls, ∿ 70 mmol) which was vigorously stirred (magnetic bar) and immersed in a room temperature water bath. An immediate yellow precipitate formed with each drop. The reaction mixture was allowed to stir overnight. The dropwise addition of H_2O (75 ml) hydrolyzed the boron compounds. After 3-6 hr hydrolysis time, a light tan solid was collected by filtration and washed well with H_2O. The crude product was slurried in H_2O (150 ml), aq. NaOH was added to achieve a pH ∿ 7 solution, which was clarified by filtration through Celite. The addition of aq. HCl gave a flocculent precipitate. This was collected by filtration, washed well with H_2O and dried over P_2O_5 (in

vacuo, room temperature, 48 hr). Thus was obtained amorphous tan powder 8·3 H_2O (3.6 g, 67%): mp 230-40° (glass); ir (KBr) 3600-3300 (-OH), 2600-2400 (COOH), 1675 (-COOH), 1605 (-CONH-), 1450, 1320, 1225, 1175, 740 cm^{-1}; ^{1}HNMR (DMSO·D_2O) δ 1.5-2.5 (broad m, 8H, NCH_2CH_2-), 3.3-4.3 (broad m, 12H, N-CH_2-), 7.0-8.0 (broad m, 8H, ArH).

Anal. ($C_{42}H_{42}N_4O_{20}\cdot 3H_2O$) C, H, N.

N,N',N"-tris(2,3-dihydroxy-4-carboxybenzoyl)-1,5,10-triazadecane (10). Using the same procedure as for 8, the following ingredients were combined: 9 (6.5 g, 8 mmol) dissolved in CCl_4 (75 ml) and BBr_3 (8 ml, 80 mmol) dissolved in CH_2Cl_2 (175 ml). Hydrolysis of the boron compounds, filtration, water wash, acid-base precipitation and drying over P_2O_5 (as before) gave amorphous tan powder 10·2.5 H_2O (4.1 g, 71%): mp 235-45°d; ir (KBr) 3600-3200 (OH), 2600-2400 (COOH), 1680 (COOH), 1610 (-CONR-), 1455, 1325, 1230, 1180, 745 cm^{-1}; ^{1}HNMR (DMSO·D_2O) δ 1.2-2.2 (broad m, 6H, N-CH_2CH_2-), 3.1-4.2 (broad m, 8H, N-CH_2-), 7.1-7.7 (broad m, 6H, ArH).

Anal. ($C_{31}H_{31}N_3O_{15}\cdot 2\text{-}1/2\ H_2O$) C, H, N.

Biological Results and Discussion

The general procedures used have been described in detail elsewhere.[6] All solutions tested were isotonic in saline at pH 7. Animal experiments were carried out on groups of five adult female mice (35 g), injected first with ^{238}Pu citrate (about 1.5 μCi/kg, i.v.) followed one hour later by a single 20 to 30 μmol/kg bw (i.p.) dose of test compound. Radioactivity measurements (whole body counts) were made at injection and 24 hr later.

One group of mice received compound (8), another, (10), and a control group, isotonic saline. The counts showed 27%, 51%, and 94% retention of plutonium, respectively. Continued administration of ten daily injections of compound (8) for 14 days produced no grossly observable signs of toxicity.

These initial animal experiments indicate that the 4-carboxylate tetramer (8) is even more effective in promoting plutonium excretion than the corresponding 5-sulfonate derivative[17] (35% retention), which was previously tested and reported as the most effective compound to date.[6] There is also a strong correlation of the Pu removal capability and the number of substituted DHB groups in the molecule: the monomeric catechol carboxylate is ineffective as a Pu removal agent; a dimer has not been tested; the trimer removes 49%; the tetramer removes 73%. These single-dose results are consistent with the hypothesis that a chelate able to provide an eight-coordinate metal ion environment will be most effective as a Pu(IV) removal agent.

It is also pertinent that the 4-CO_2^- substituent not only increases the solubility of these compounds but is potentially a ligating group as well, which is not true of the 5-SO_3^- groups of the previous compounds. Finally, a 0.2 mM solution of trimeric (10) removes Fe(III) from iron-saturated human transferrin with an apparent first-order rate constant of 2.1×10^{-3} min^{-1}, which is essentially the same rate as enterobactin.[18] This shows that these carboxylate-substituted compounds are both kinetically and thermodynamically capable of removing iron from this iron transport protein.

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References

1. This is paper number 5 in the series "Ferric Ion Sequestering Agents and also number 5 in the series "Specific Sequestering Agents for the Actinides." For previous papers in these series see reference 3 and 6, respectively.

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   c) Biology and Medicine Division, Lawrence Berkeley Laboratory.

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Appendix to Experimental

Compound 2; Anal. Calcd for $C_8H_4O_6Na_2$: Na, 18.99. Found: Na, 18.80.

Compound 5; Anal. Calcd for $C_{11}H_{11}O_6Na$: C, 50.39; H, 4.23; Na, 8.77. Found: C, 50.05; H, 4.37; Na, 8.82.

Compound 7; Anal. Calcd for $C_{54}H_{66}N_4O_{20}\cdot 2/3\ CCl_4$: C, 55.01; H, 5.57; N, 4.69. Found: C, 54.93; H, 5.75; N, 4.64.

Compound 9; Anal. Calcd for $C_{40}H_{49}N_3O_{15}\cdot 1/2\ CCl_4$: C, 54.73; H, 5.56; N, 4.72. Found: C, 54.86; H, 5.71; N, 4.69.

Compound 8; Anal. Calcd for $C_{42}H_{42}N_4O_{20}\cdot 3\ H_2O$: C, 51.64; H, 4.95; N, 5.74. Found: C, 51.44; H, 4.72; N, 5.62.

Compound 10; Anal. Calcd for $C_{31}H_{31}N_3O_{15}\cdot 2.5\ H_2O$: C, 50.96; H, 4.97; N, 5.74. Found: C, 50.80; H, 4.87; N, 5.60.

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Compound 7; ($C_{54}H_{66}N_4O_{20}$); m/e 1091 (molecular ion)

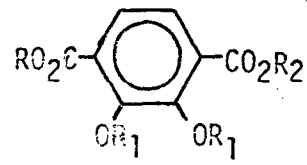
Compound 8: ($C_{42}H_{42}N_4O_{20}$); m/e 923 (molecular ion)

Compound 9: ($C_{40}H_{49}N_3O_{15}$); m/e 812 (molecular ion)

Compound 10: ($C_{31}H_{31}N_3O_{15}$); m/e 686 (molecular ion)

TABLE I.

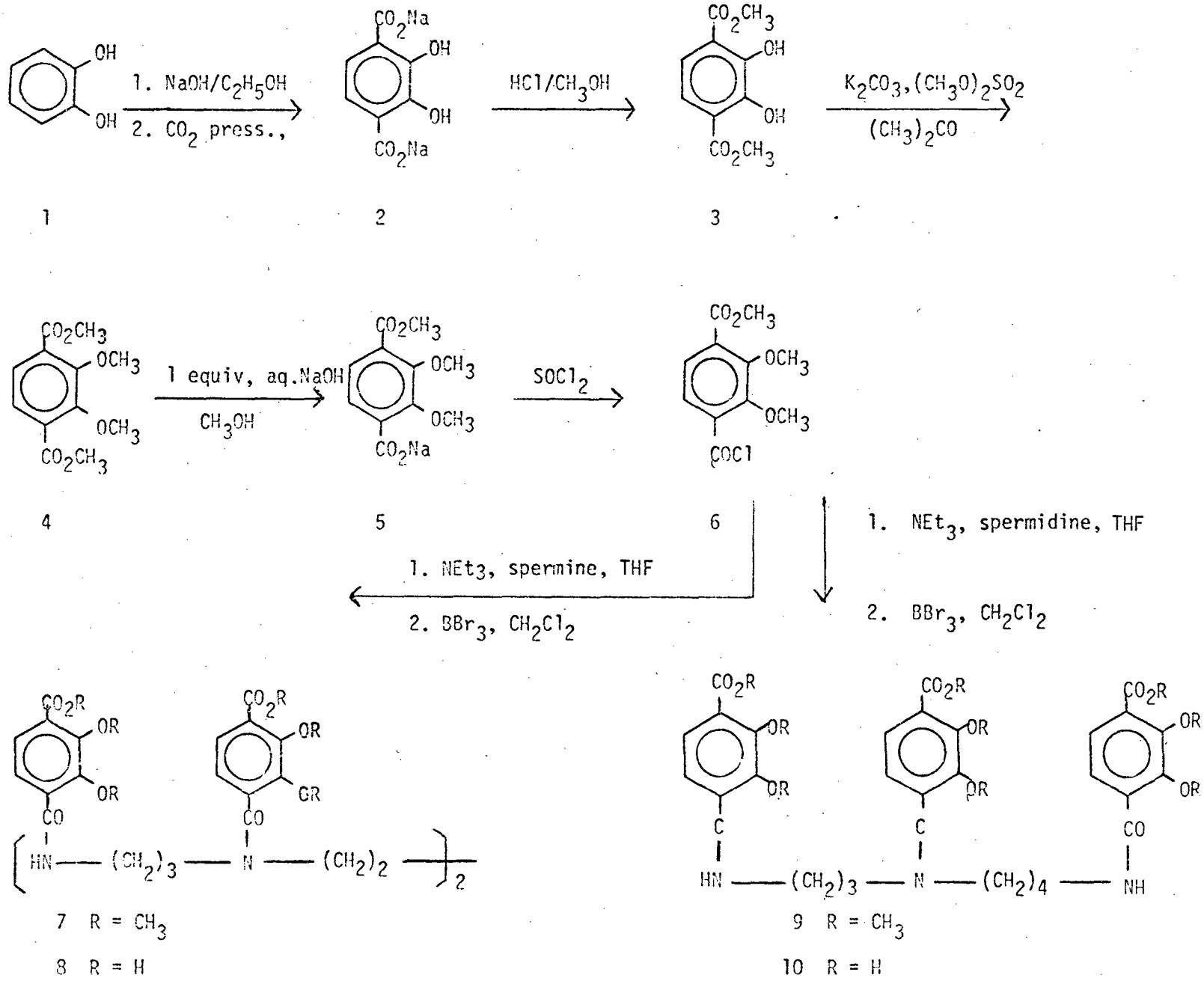
Monomeric 2,3-Dihydroxyterephthalic Acid Derivatives



no.	R	R_1	R_2	mp or bp (mm), °C	% yield	recrystn solvent	emp formula[a]
2	Na	H	Na	>300	24	H_2O	$C_8H_4O_6Na_2$
2a	H	H	H	289-90d[b]	35		$C_8H_6O_6$
3	CH_3	H	CH_3	141-3[c]	82	CH_3OH	$C_{10}H_{10}O_6$
4	CH_3	CH_3	CH_3	130(0.4)[d]	68		$C_{12}H_{14}O_6$
5	CH_3	CH_3	Na	205-7	68	CH_3OH/acetone/ether	$C_{11}H_{11}O_6Na$
6	CH_3	CH_3	Cl	e	100	CCl_4	$C_{11}H_{11}O_6Cl$

[a] Analyses for C,H, Na are within 0.4% of theoretical values. [b] Lit. mp 293°; see ref 20. [c] Lit. mp 145-6°, see ref 21. [d] Lit. b_5 165°, see ref 21. [e] Used as a crude, dry, crystalline solid without further purification, see Experimental Section.

Scheme I.


1. NaOH/C2H5OH
2. CO2 press.,
HCl/CH3OH
K2CO3,(CH3O)2SO2
(CH3)2CO
1 equiv, aq.NaOH
CH3OH
SOCl2
1. NEt3, spermine, THF
2. BBr3, CH2Cl2
1. NEt3, spermidine, THF
2. BBr3, CH2Cl2
1
2
3
4
5
6
7 R = CH3
8 R = H
9 R = CH3
10 R = H

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