cause they interfere with tonic dopaminergic inhibition of prolactin release (6). Previous work showed that spiperone, one of the most potent dopamine receptor antagonists, elevates plasma prolactin levels in rats (3). In the present study, prolactin levels were elevated significantly 30 min after the administration of a low dose of this neuroleptic to male rats (Table II). As shown in Table II, the same low dose of *p*-bromospiperone resulted in a comparable rise in serum prolactin levels. These results indicate that the bromination of the spiperone molecule does not significantly affect its ability to act as a dopamine receptor blocker in pituitary receptors *in vivo*, a finding consistent with results from the *in vitro* binding study. This brominated analog thus has potential as a neuroleptic drug. In addition, the radiobrominated compound may prove to be an extremely useful pharmacological tool for dopamine receptor studies in humans using positron emission tomography.

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New Compounds: N^1,N^8-Bis(2,3-dihydroxybenzoyl)spermidine and Analogs as Potential Iron-Chelating Drugs

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Abstract □ N^1,N^8-Bis(2,3-dihydroxybenzoyl)spermidine was synthesized and evaluated as an iron-chelating drug. Homologs were prepared and evaluated together with a series of *N,N'*-bis(2,3-dihydroxybenzoyl)-α,ω-diaminoalkanes. Analogous 2-hydroxybenzoyl compounds also were synthesized and evaluated.

Keyphrases □ N^1,N^8-Bis(2,3-dihydroxybenzoyl)spermidine—synthesis and evaluation as iron-chelating drug □ Chelating agents—N^1,N^8-bis(2,3-dihydroxybenzoyl)spermidine and analogs, synthesis and evaluation as iron-sequestering agents

An orally effective, iron-chelating drug is needed to treat patients with Cooley's anemia. Patients suffering from this genetic disease must be transfused every 2–4 weeks. Since the body lacks a physiological means of excreting the iron present in transfused erythrocytes, these patients develop a secondary iron overload, which leads to damage of vital organs and eventually to death. It was suggested that 2,3-dihydroxybenzoic acid might be an orally effective, iron-chelating drug (1). Although subsequent clinical evaluation confirmed this report (2–4), it was not possible to maintain patients in iron balance.

A chelating agent with a greater affinity for iron presumably would be more effective. Several iron-sequestering agents produced by microbes are conjugates of 2,3-dihydroxybenzoic acid (5–9). These compounds all possess affinities for iron that are many orders of magnitude greater than the affinity of the parent compound. One of these compounds, N^1,N^8-bis(2,3-dihydroxybenzoyl)spermidine (8), removes iron from the ferritin of cultured Chang cells and from transferrin, the principal iron-binding protein of serum (10).

The synthesis of N^1,N^8-bis(2,3-dihydroxybenzoyl)-spermidine hydrochloride (XVII) together with a series of simpler analogs is presented in this report. Preliminary evidence suggests that this type of compound may be useful in iron-chelation therapy whereas the corresponding 2-hydroxybenzoyl derivatives are inactive. The *in vitro* and *in vivo* evaluation of these compounds will be presented later.

DISCUSSION

Prior to the synthesis of XVII, a series of simpler analogs, *i.e.*, *N,N'*-bis(2,3-dihydroxybenzoyl)-α,ω-diaminoalkanes, was prepared. Like the spermidine derivative, these compounds would be expected to bind iron strongly, their affinities for iron and perhaps their biological activities being related to the separation of the 2,3-dihydroxybenzoyl moieties. The compounds were obtained readily in a 40–50% yield *via* the reaction of 2,3-dioxosulfinylbenzoyl chloride (11) with the appropriate α,ω-diaminoalkane in tetrahydrofuran (Procedure A). Since the goal of this program was to obtain enough pure material for biological testing, no attempt was made to optimize the yield of this or subsequent reactions.

All compounds were obtained as solids which were purified by recrystallization. The ethane (I) and propane (II) derivatives were somewhat unique in that they were crystallized from aqueous methanol as their hydrates. Compound I was obtained as a monohydrate, with the water of crystallization being lost upon drying under vacuum at 78° for 4 hr. Compound II was obtained from aqueous methanol as the dihydrate. Drying caused the loss of both moles of water, as evidenced by elemental analysis.

The identity of I, II, and V was confirmed *via* independent synthesis. Two moles of 2,3-diacetoxybenzoic acid were condensed with ethylenediamine, 1,3-diaminopropane, or 1,6-diaminohexane *via* activation with *N,N'*-dicyclohexylcarbodiimide (Procedure B). Subsequent hydrolysis of the protecting groups yielded products (40%) identical to those obtained by Procedure A. Compound II also was prepared by fusing methyl 2,3-dihydroxybenzoate and 1,3-diaminopropane at 130° under nitrogen (Procedure C). The latter procedure was used to prepare an analogous series of *N,N'*-bis(2-hydroxybenzoyl)-α,ω-diaminoalkanes (X–XIV).

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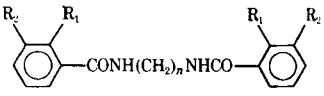
Table I—Physical Constants of *N,N'*-Bis(aroyl)-α,ω-diaminoalkanes



Compound	*n*	R_1	R_2	Method	Yield, %	Melting Point	Recrystallization Solvent	Formula	Analysis, %	Calc.	Found
I	2	OH	OH	A	43	220–221°	Aqueous methanol	$C_{16}H_{16}N_2O_6$	C	57.83	57.63
				B	41				H	4.85	4.86
									N	8.43	8.30
II	3	OH	OH	C	42	168–169°	Aqueous methanol	$C_{17}H_{18}N_2O_6$	C	58.95	59.26
				A	59				H	5.24	5.27
				B	44				N	8.09	8.14
III	4	OH	OH	A	45	210–212°	Aqueous methanol	$C_{18}H_{20}N_2O_6$	C	59.99	59.82
									H	5.59	5.55
									N	7.77	7.70
IV	5	OH	OH	A	40	174–176°	Aqueous methanol	$C_{19}H_{22}N_2O_6$	C	60.95	60.66
									H	5.92	5.95
									N	7.48	7.30
V	6	OH	OH	A	55	184–186°	Aqueous ethanol	$C_{20}H_{24}N_2O_6$	C	61.84	61.69
				B	38				H	6.23	6.24
									N	7.21	7.17
VI	8	OH	OH	A	38	172–174°	Ethyl acetate–petroleum ether	$C_{22}H_{28}N_2O_6$	C	63.45	63.22
									H	6.78	6.70
									N	6.73	6.59
VII	9	OH	OH	A	53	146–147°	Ethyl acetate–petroleum ether	$C_{23}H_{30}N_2O_6$	C	64.16	64.26
									H	7.02	7.04
									N	6.50	6.46
VIII	10	OH	OH	A	51	148–150°	Ethyl acetate–petroleum ether	$C_{24}H_{32}N_2O_6$	C	64.86	64.66
									H	7.20	7.22
									N	6.30	6.26
IX	12	OH	OH	A	54	130–131°	Ethyl acetate–petroleum ether	$C_{26}H_{36}N_2O_6$	C	66.08	66.37
									H	7.68	7.77
									N	5.93	5.94
X	2	OH	H	C	46	187–189°	Ethanol	$C_{16}H_{16}N_2O_4$	C	63.99	64.01
									H	5.37	5.41
									N	9.33	9.34
XI	3	OH	H	C	38	181–182.5°	Ethanol	$C_{17}H_{18}N_2O_4$	C	64.95	65.00
									H	5.77	5.71
									N	8.91	8.79
XII	4	OH	H	C	42	180–181°	Ethanol	$C_{18}H_{20}N_2O_4$	C	65.84	65.91
									H	6.14	6.15
									N	8.53	8.56
XIII	6	OH	H	C	45	141–142.5°	Ethanol	$C_{20}H_{24}N_2O_4$	C	67.39	67.36
									H	6.79	6.73
									N	7.87	7.84
XIV	8	OH	H	C	49	139–140.5°	Ethanol	$C_{22}H_{28}N_2O_4$	C	68.72	68.70
									H	7.34	7.44
									N	7.29	7.32

These compounds chelated iron but failed to induce significant amounts of iron excretion when given intraperitoneally to hypertransfused rats.

Attempts to prepare N^1,N^8-bis(2,3-dihydroxybenzoyl)spermidine *via* Procedure A met with little success. Mixtures were obtained from which the desired compound could not be isolated. The hydrochloride salt (XVII) ultimately was prepared in low yield (14%) *via* treatment of the fusion products of spermidine and methyl 2,3-dihydroxybenzoate with hydrogen chloride (Procedure D). While purification of the free amine proved difficult, the hydrochloride could be purified readily by recrystallization from water. In similar fashion, the corresponding derivatives of diethylenetriamine and 3,3'-diaminodipropylamine were prepared. These hydrochlorides were obtained as the hydrates from which the water was removed upon drying *in vacuo*. N^1,N^5-Bis(2-hydroxybenzoyl)diethylenetriamine (XVIII) also was prepared. This compound was readily obtained as the free amine using Procedure C.

EXPERIMENTAL[1]

Methyl salicylate, 2,3-dihydroxybenzoic acid, *N,N'*-dicyclohexylcarbodiimide, and all of the diamines and triamines were obtained commercially. Methyl 2,3-dihydroxybenzoate was prepared according to the method of Clinton and Laskowski (12), whereas 2,3-diacetoxybenzoic acid was synthesized as described by Simokoriyama (13).

Preparation of Conjugated Derivatives—The general procedures for synthesis of *N,N'*-bis(aroyl)-α,ω-diaminoalkanes and *N,N'*-bis(aroyl)-ω,ω'-diaminodialkylamines are described as follows. The physical constants observed together with the analytical data are summarized in Tables I and II.

Procedure A—A mixture of 15.4 g (0.1 mole) of 2,3-dihydroxybenzoic acid and 35 ml (0.5 mole) of thionyl chloride was heated under reflux for 8 hr. Upon cooling, the residual thionyl chloride was removed under vacuum. To the residue was added ~10 ml of anhydrous benzene, which was evaporated under vacuum. This process was repeated three times.

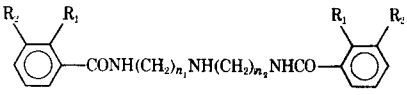
The solid residue containing 2,3-dioxosulfinylbenzoyl chloride (11) then was dissolved in 200 ml of tetrahydrofuran. To this solution were added 0.04 mole of the diamine and 30 g (0.22 mole) of anhydrous potassium carbonate. The reaction mixture was heated under reflux for 12 hr, cooled, and filtered to remove potassium salts. After evaporation of the solvent, 250 ml of water was added and the mixture was allowed to stand at room temperature for 5–6 hr. After the water was decanted, the residue was recrystallized from aqueous methanol.

Procedure B—A solution of 2.1 g (0.01 mole) of *N,N'*-dicyclohexylcarbodiimide and 4.76 g (0.02 mole) of 2,3-diacetoxybenzoic acid in 200 ml of acetonitrile containing 2 ml of pyridine was stirred at room temperature for 2 hr. The precipitated dicyclohexylurea was removed by filtration, and 0.005 mole of the diamine and 1.75 ml (0.0125 mole) of triethylamine were added. The reaction mixture was allowed to stir overnight at room temperature under nitrogen.

The solvent was evaporated under reduced pressure, and the residue

[1] Melting points were determined with a capillary melting-point apparatus and are uncorrected. TLC was carried out on silica gel with benzene–methanol–acetic acid (45:8:1) as the eluent. Compounds were visualized by spraying first with 0.5% ferric chloride and then with either 1% basic permanganate reagent or 50% H_2SO_4 (charred). For identification, NMR spectra were determined at 60 MHz in acetone-d_6 or dimethyl sulfoxide-d_6 containing a few drops of deuterium oxide. In all cases, the integrals and chemical shifts were in agreement with those expected. The spectra of representative compounds (V, XIII, and XVII) were determined at 220 MHz in dimethyl sulfoxide-d_6 containing deuterium oxide. Values are reported in parts per million (δ) downfield from tetramethylsilane (the internal standard).

Table II—Physical Constants of *N,N'*-Bis(aroyl)-ω,ω'-diaminodialkylamines



Compound	n_1	n_2	R_1	R_2	Method	Yield, %	Melting Point	Recrystallization Solvent	Formula	Analysis, %	Calc.	Found
XV	2	2	OH	OH	D	18	163–165°	Water	$C_{17}H_{21}N_3O_6$·HCl	C	52.49	52.51
										H	5.34	5.28
										N	10.20	10.12
XVI	3	3	OH	OH	D	16	115–117°	Water	$C_{19}H_{25}N_3O_6$·HCl	C	54.69	54.62
										H	5.95	6.02
										N	9.55	9.31
XVII	3	4	OH	OH	D	14	205–207°	Water	$C_{20}H_{27}N_3O_6$·HCl	C	55.56	55.33
										H	6.17	6.02
										N	9.26	8.98
XVIII	2	2	OH	H	C	37	151.5–153°	Ethanol	$C_{18}H_{21}N_3O_4$	C	62.96	63.02
										H	6.16	6.09
										N	12.24	12.27

was taken up in ethyl acetate. This solution was washed with 10% HCl (two times), 10% $NaHCO_3$, and water. The solvent was evaporated, leaving a residual semisolid, which then was dissolved in methanol (30 ml) to which was added 10 ml of 4 *N* NaOH. This solution was stirred under nitrogen at room temperature for 1 hr, after which it was acidified with 10% HCl. The solvent was evaporated, and the residue was crystallized from aqueous methanol.

Procedure C—To a 50-ml, round-bottom flask were added 21 g (17.9 ml, 0.138 mole) of methyl salicylate and 0.067 mole of the diamine (or triamine). An immediate reaction took place with generation of heat. Precipitation often ensued. The reaction mixture then was heated under nitrogen at 130° for 3 hr. Upon cooling, the residue was recrystallized from 95% ethanol.

Procedure D—To a 100-ml, round-bottom flask were added 0.03 mole of the triamine and 0.06 mole of methyl 2,3-dihydroxybenzoate. This mixture was heated under nitrogen at 130–140° for 3 hr. Upon cooling, the viscous residue was dissolved in 200 ml of methanol. The resulting solution was concentrated to ~50 ml and poured into 200 ml of anhydrous ether.

After stirring at room temperature for 30 min, the precipitate was collected by suction filtration and dissolved in 200 ml of methanol. This solution was saturated with hydrogen chloride, concentrated to ~50 ml, and poured into 200 ml of anhydrous ether. After stirring for 30 min, the ether was decanted and the residue was recrystallized from water.

***N,N'*-Bis(2,3-dihydroxybenzoyl)ethylenediamine (I)**—Compound I was prepared according to Procedure A. The solid obtained was recrystallized twice from aqueous methanol to yield 7.6 g (43%) of I as tiny tan needles, which were pure as evidenced by TLC. Elemental analysis revealed that the material was a monohydrate. Drying *in vacuo* at 78° for 8 hr caused loss of the water of crystallization.

Compound I also was prepared according to Procedure B. The synthesis was carried out as described, except that pyridine was used in place of triethylamine. The semisolid obtained was recrystallized from aqueous methanol to yield 0.72 g (41%) of light-tan needles, mp 220–221°. The melting point was not depressed upon admixture with the sample prepared according to Procedure A. TLC and the NMR spectra showed that the two samples were identical. Elemental analysis of a sample dried at 78° for 8 hr verified it as $C_{16}H_{16}N_2O_6$.

***N,N'*-Bis(2,3-dihydroxybenzoyl)-1,3-diaminopropane (II)**—Compound II was prepared by Procedure C. Upon cooling, the reaction mixture was dissolved in ethanol (50 ml). This solution was poured into 50 ml of water containing a few drops of acetic acid. After stirring at room temperature for 30 min, the solid (6.3 g) was collected by filtration. TLC showed that this solid was nearly pure; it was contaminated with a small amount of methyl 2,3-dihydroxybenzoate together with traces of the mono adduct. Addition of more water to the filtrate gave additional product, but it was very impure.

The solid (6.3 g) was dissolved in 25 ml of ethanol and decolorized with charcoal. Addition of 25 ml of water to the pale-orange solution yielded the desired compound upon cooling. The pink needles (4.8 g, 42%) melted over a wide range, depending on the rate of heating. Elemental analysis revealed that the compound contained 2 moles of water. After drying at 78° for 6 hr, the compound melted at 168–169°. Both moles of water were lost after drying, as evidenced by elemental analysis.

A second sample of II was prepared by Procedure A. The semisolid obtained was recrystallized twice from aqueous methanol to yield 9.0 g (59%) of II. TLC revealed that the material was pure and that it cochromatographed with a sample of the material prepared by Procedure C.

This compound also was synthesized from 2,3-diacetoxybenzoic acid according to Procedure B. The semisolid obtained was recrystallized twice from aqueous methanol to yield 0.85 g (44%) of tiny pink needles. TLC revealed that the material was pure and that it cochromatographed with the product obtained *via* Procedure C. The melting point of a sample dried *in vacuo* at 78° for 4 hr and admixed with a similar sample prepared according to Procedure C was not depressed. Likewise, the NMR spectrum was identical to that of a sample prepared according to Procedure C.

***N,N'*-Bis(2,3-dihydroxybenzoyl)-1,4-diaminobutane (III)**—Compound III was prepared according to Procedure A. The semisolid obtained was crystallized from aqueous ethanol and then was recrystallized from aqueous methanol to yield 5.8 g (45%) of III as an amorphous tan solid, mp 210–212°. The NMR spectrum and elemental analysis were in agreement with those expected.

***N,N'*-Bis(2,3-dihydroxybenzoyl)-1,5-diaminopentane (IV)**—Compound IV was prepared according to Procedure A. The semisolid residue was dissolved in ethyl acetate and then extracted with 10% $NaHCO_3$, water, and saturated sodium chloride. After drying over anhydrous magnesium sulfate, the ethyl acetate was removed *in vacuo*. The residual solid was recrystallized from aqueous methanol to give 5.8 g (40%) of IV as an amorphous tan solid, mp 174–176°.

***N,N'*-Bis(2,3-dihydroxybenzoyl)-1,6-diaminohexane (V)**—Compound V was synthesized *via* Procedure A. The reaction product was recrystallized twice from aqueous ethanol, yielding 8.3 g (55%) of a cream-colored amorphous solid, mp 184–186°; NMR (dimethyl sulfoxide-d_6–deuterium oxide): δ 7.26 [dd, 2H, $^3J(H^6\text{–}H^5) \simeq 8.1$, $^4J(H^6\text{–}H^4) \simeq 1.2$, aromatic C_6-H], 6.93 [dd, 2H, $^3J(H^5\text{–}H^6) \simeq 7.9$, $^4J(H^4\text{–}H^6) \simeq 1.2$, aromatic C_4-H], 6.69 [m, 2H, $^3J(H^5\text{–}H^4) \simeq {}^3J(H^5\text{–}H^6) \simeq 7.9$, $^4J(H^4\text{–}H^6) \simeq 1.2$, aromatic C_5-H], 3.28 (m, 4H, $J \simeq 6.8$, $NHCH_2$), 1.54 (m, 4H, $NHCH_2CH_2$), and 1.34 (m, 4H, $NHCH_2CH_2CH_2$).

Compound V also was synthesized by Procedure B. Pyridine was employed rather than triethylamine. The product obtained was recrystallized twice from aqueous methanol, yielding 0.73 g (38%) of a light-tan solid, mp 184–186°. The mixed melting point of this product with that obtained *via* Procedure A was not depressed. TLC and NMR spectroscopy revealed that the two compounds were identical.

***N,N'*-Bis(2,3-dihydroxybenzoyl)-1,8-diaminooctane (VI)**—Compound VI was prepared according to Procedure A. The reaction product was taken up in ethyl acetate and washed successively with 10% $NaHCO_3$ (twice), water, and saturated sodium chloride. Recrystallization (twice) from ethyl acetate–petroleum ether (60–90°) gave 6.4 g (38%) of tan crystals, mp 172–174°.

***N,N'*-Bis(2,3-dihydroxybenzoyl)-1,9-diaminononane (VII)**—Compound VII was prepared exactly as was VI using Procedure A. The compound was isolated (9.2 g, 53%) as tiny cream-colored needles after recrystallization (twice) from ethyl acetate–petroleum ether (60–90°). The NMR spectrum and elemental analysis were in agreement with the theory.

***N,N'*-Bis(2,3-dihydroxybenzoyl)-1,10-diaminodecane (VIII)**—Compound VIII was prepared exactly as was VI using Procedure A. The product was obtained (9.1 g, 51%) as a tan powder, mp 148–150°. TLC revealed that the material was pure. The elemental analysis and the NMR spectrum were in agreement.

***N,N'*-Bis(2,3-dihydroxybenzoyl)-1,12-diaminododecane (IX)**—Compound IX was prepared as was VI using Procedure A. The product

(10.2 g, 54%) was obtained as a cream-colored powder, mp 130–131°. The NMR spectrum agreed with that expected.

***N,N'*-Bis(2-hydroxybenzoyl)ethylenediamine (X)**—Compound X was prepared according to Procedure C. The reaction mixture was dissolved in methanol, and this solution then was poured into ether. After stirring at room temperature for 1 hr, the solid was collected by filtration. This solid was recrystallized from ethanol to give 8.3 g (46%) of cream-colored crystals, mp 187–189°.

***N,N'*-Bis(2-hydroxybenzoyl)-1,3-diaminopropane (XI)**—Compound XI was prepared according to Procedure C. Upon cooling, the reaction mixture was dissolved in 50 ml of methanol. To this solution was added 50 ml of water containing a few drops of acetic acid. Upon stirring at room temperature, the oily precipitate solidified. The solid (13.5 g) was recrystallized twice from ethanol (100 ml) to yield 7.2 g (38%) of white crystals, which were pure by TLC, mp 181–182.5°.

***N,N'*-Bis(2-hydroxybenzoyl)-1,4-diaminobutane (XII)**—Compound XII was prepared according to Procedure C. The solid reaction mixture was dissolved in methanol, and the product was precipitated *via* the addition of water. The product (15.9 g) was recrystallized from ethanol (75 ml) to yield 8.2 g (42%) of shiny white plates, which were pure by TLC, mp 180–181°.

***N,N'*-Bis(2-hydroxybenzoyl)-1,6-diaminohexane (XIII)**—Compound XIII was prepared according to Procedure C. The waxy solid residue was crystallized from 35 ml of ethanol, yielding 10.9 g of product. TLC showed that this product contained some of the mono adduct. Recrystallization from ethanol gave 9.7 g (45%) of pure product as waxy white plates, mp 141–142.5°; NMR (dimethyl sulfoxide-d_6–deuterium oxide): δ 7.82 [dd, 2H, $^3J(H^6\text{–}H^5) \simeq 8.1$, $^4J(H^6\text{–}H^4) \simeq 1.3$, aromatic C_6-H], 7.41 [m, 2H, $^3J(H^4\text{–}H^3) \simeq {}^3J(H^4\text{–}H^5) \simeq 7.7$, aromatic C_4-H], 6.90 [m, 4H, $^3J(H^3\text{–}H^4) \simeq {}^3J(H^5\text{–}H^4) \simeq {}^3J(H^5\text{–}H^6) \simeq 7.9$, aromatic C_5-H and C_3-H], 3.31 (m, 4H, $J \simeq 6.8$, $NHCH_2$), 1.57 (m, 4H, $NHCH_2CH_2$), and 1.36 (m, 4H, $NHCH_2CH_2CH_2$).

***N,N'*-Bis(2-hydroxybenzoyl)-1,8-diaminooctane (XIV)**—Compound XIV was prepared according to Procedure C. The solid reaction mixture was crystallized from ethanol (50 ml), yielding 12.5 g of product. TLC revealed that this product contained a small amount of the mono adduct. Recrystallization from ethanol gave 11.4 g (49%) of product as waxy white plates, mp 139–140.5°.

***N*^{1},*N*^{5}-Bis(2,3-dihydroxybenzoyl)diethylenetriamine Hydrochloride (XV)**—Compound XV was prepared *via* Procedure D from 5.2 g (0.05 mole) of diethylenetriamine and 16.0 g (0.10 mole) of methyl 2,3-dihydroxybenzoate. The hydrochloride was obtained as a cream-colored powder (3.8 g, 18%), mp 163–165°.

***N*^{1},*N*^{7}-Bis(2,3-dihydroxybenzoyl) -3,3'- diaminodipropylamine Hydrochloride (XVI)**—Compound XVI was prepared according to Procedure D exactly as was XV. The hydrochloride was isolated as a cream-colored powder (2.6 g, 16%). After drying at 78° for 4 hr, the elemental analysis confirmed its formula as $C_{19}H_{25}N_3O_6$·HCl. This material failed to melt sharply; a phase transition occurred at 85–87°, after which it melted with decomposition at 115–117°.

***N*^{1},*N*^{8}-Bis(2,3-dihydroxybenzoyl)spermidine Hydrochloride (XVII)**—Compound XVII was prepared by Procedure D from 5 g (0.034 mole) of spermidine and 11.6 g (0.07 mole) of methyl 2,3-dihydroxybenzoate. The product was obtained as a light-tan powder (2.2 g, 14%), mp 205–207°. TLC revealed that the compound was pure. After drying at 78° for 6 hr, the compound was free from the water of crystallization as evidenced by elemental analysis. The NMR spectrum of the hydrochloride (dimethyl sulfoxide-d_6–deuterium oxide) gave the following values: δ 7.31 [m, 2H, $^3J(H^6\text{–}H^5) \simeq 7.7$, $^4J(H^6\text{–}H^4) < 1.0$, aromatic C_6-H], 6.95 [d, 2H, $^3J(H^4\text{–}H^5) \simeq 7.9$, $^4J(H^4\text{–}H^6) < 1.0$, aromatic C_4-H], 6.70 [m, 2H, $^3J(H^5\text{–}H^4) \simeq {}^3J(H^5\text{–}H^6) \simeq 7.9$, aromatic C_5-H], 3.36 (m, 4H, $CONHCH_2$), 2.93 (m, 4H, CH_2NHCH_2), 1.91 (m, 2H, $NHCH_2CH_2CH_2NH$), and 1.64 (m, 4H, $NHCH_2CH_2CH_2CH_2NH$).

***N*^{1},*N*^{5}-Bis(2-hydroxybenzoyl)diethylenetriamine (XVIII)**—Compound XVIII was prepared according to Procedure C. Upon cooling, the reaction mixture solidified as a glass. This solid was triturated with methanol from which 14.3 g of solid separated. The solid was recrystallized from ethanol to yield 8.4 g (37%) of slightly orange crystals, mp 151.5–153°. The NMR spectrum and elemental analysis were in agreement with those expected.

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