Pergamon

Tetrahedron, Vol. 52, No. 34, pp. 11177-11214, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00668-0

Heterocyclic Nonionic X-Ray Contrast Agents V: A Facile Conversion of 2-Tetrahydrofuroamides into α-Hydroxy-δ-valerolactams and a General Synthesis of Lactams Conjugated to 2,4,6-Triiodoisophthalamides[¥]

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¥Presented at the 204th ACS National Meeting, Washington, D.C., August 22-28, 1992; ORGN106

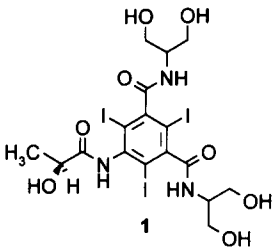
ABSTRACT: The synthesis of 2,4,6-triiodoisophthalamides substituted by a lactam moiety is described. A tandem ring opening-ring closure methodology consisting of a regiospecific ether cleavage of the tetrahydrofuroanilide **14b**, followed by lactamization to α-oxygenated anilides **15b** or **16b**, gave α-O-functionalized-δ-valerolactams **12b** or **13b**, respectively. This approach is also compatible with the presence of ester and carbonyl chloride functions on the triiodophenyl moiety. A general synthesis of lactams **34-39** was also achieved. Further chemical modifications led to water soluble unsubstituted-lactams (**34d**, **35d**, **37d**) and α-hydroxy-lactams [**42(d,e)**, **13(d,e)** and **43d**] that are of interest as X-ray contrast agents.

INTRODUCTION

In parts I-IV[1a-d] of this series we presented the rationale for designing X-ray contrast agents based on the attachment of heterocyclic moieties at the 5 position of the aromatic ring. The main aim was to develop new and improved nonionic contrast media (NICM) having greater stability and lower osmolality than currently employed radiographic agents such as iopamidol **(1)**[2], iohexol **(2)**[3] and diatrizoic acid **(3)**[4]. We demonstrated that several of the heterocyclically modified triiodobenzenoids possessed better water solubility, stability, and osmolality characteristics and that these properties were dependent on the nature of the heterocyclic moiety present.

In this paper we describe the synthesis of NICM candidates (**13**, **34**, **35**, **37**, **42**, and **43**) bearing a lactam moiety at the 5 position of the 2,4,6-triiodo-isophthalamide moiety. The rationale was that variations in substitution and/or ring size of the lactam moiety might affect the hydrophobicity parameter of the resulting contrast agents and thereby influence their self association in aqueous solution, resulting in changes in osmolality[5], a property that has been recognized[6] to be important in radiography. We also prepared the

unsymmetrically substituted isophthalamide **21**, bearing a primary carboxamide function, based on a recent report[7] claiming special lowering of osmolality for such modifications.



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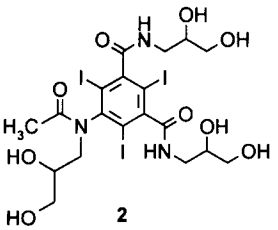

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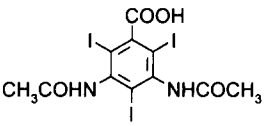

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Initially, based on design considerations developed earlier in this work, the α-hydroxy-δ-valerolactam system, present in compound **13d**, was selected as the most desirable heterocyclic moiety for obtaining target molecules with optimal properties of high water solubility, low toxicity, and low osmolality. We decided that the most practical approach to access this ring system would be to effect the regiospecific ether cleavage[8] of tetrahydrofuroyl derivatives with or without simultaneous or concomitant O-protection of the exposed hydroxyl function and then carry out the lactamization of the resulting α-O-functionalized-ω-halo-valeroyl anilides. We also anticipated that lactams of varying ring sizes and degrees of substitution could be made from 5-amino-2,4,6-triiodo-isophthalamides by acylation with appropriately substituted ω-halo-alkanoyl halides, followed by lactamization of the resulting anilides, an approach for which there is precedence in literature[9].

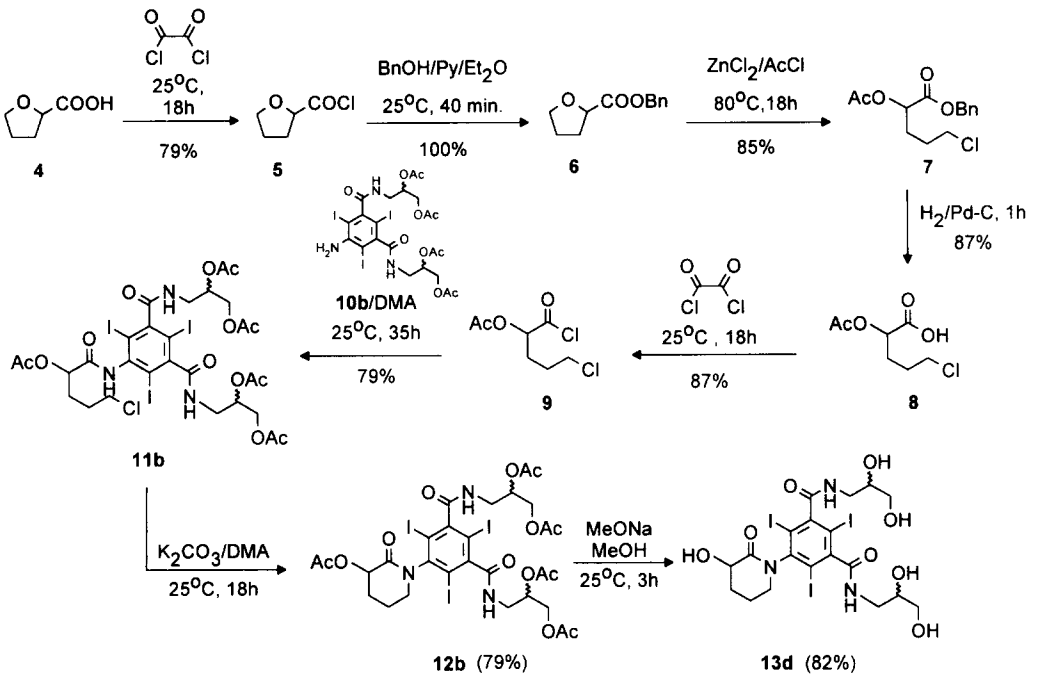
RESULTS AND DISCUSSION

Synthesis of NICM candidates based on the α-hydroxy-γ-valerolactam system

*The symmetrically substituted isophthalamide **13d**.* Short and efficient synthetic routes for the elaboration of the preferred α-hydroxy-δ-valerolactam system are depicted in Schemes 1 and 2. In these approaches the most salient feature is the use of a tandem ring opening-ring closure methodology, that exploits the 2-tetrahydrofuroyl synthon for elaborating all the carbon atoms and the oxygen atom of the α-hydroxy-δ-valerolactam system. In the first approach (Scheme 1), tetrahydro-2-furoyl chloride (**5**), prepared from tetrahydro-2-furoic acid (**4**) by treatment with oxalyl chloride in 79% yield as described[10], was treated with

benzyl alcohol in the presence of pyridine to obtain benzyl tetrahydro-2-furoate (**6**) in quantitative yield. When **6** was treated with acetyl chloride under reflux in the presence of a catalytic amount of zinc chloride[11,12],

Scheme 1



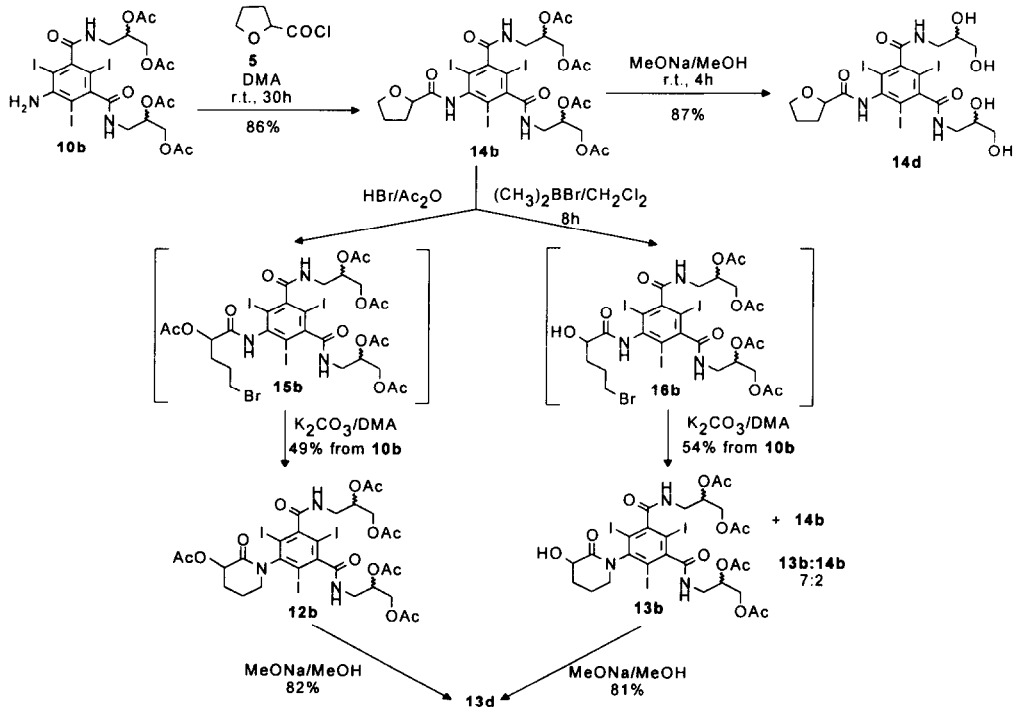
benzyl 2-acetyloxy-4-chlorovalerate (**7**) was obtained in 85% yield. The ^{1}H-NMR spectrum, which exhibited a triplet at 3.6 ppm for CH_2Cl, and a doublet of doublets at 5.2 ppm for the methine proton, was evidential. In the ^{13}C-NMR spectrum these two carbon atoms were at 44.0 ppm and 71.4 ppm, respectively. The high degree of regiospecificity observed in this ether cleavage reaction can be attributed[8] to the destabilization of the carbonium ion at C-2 with respect to the carbonium ion at C-4, due to the presence of the benzyloxycarbonyl function at C-2, thereby facilitating O-C4 bond cleavage. Despite claims[11] to the contrary, **4** failed to undergo clean ether cleavage. Attempts to cleave the acid chloride **5** with zinc chloride/acetyl chloride or hydrogen bromide/acetic anhydride[13], with the hope of obtaining the synthon **9** (or its ω-bromo congener), also failed. Catalytic hydrogenolysis (5% Pd/C) of the benzyl ester **7** in ethyl acetate-acetic acid (95:5) furnished the acid **8** in 87% yield. The use of ethanol or aqueous ethanol in this reaction resulted in 7% transesterification or 3%

hydrogenolysis, respectively. Finally, treatment of the acid **8** with oxalyl chloride furnished the desired 2-acetyloxy-4-chlorovaleroyl chloride (**9**) in 57% overall yield from **4**.

Acylation of the aniline **10b** with the acid chloride **9** gave the corresponding anilide **11b** in 79% yield, which upon lactamization furnished the fully protected α-acetyloxy-δ-valerolactam **12b** in 79% yield. Deacetylation of **12b** by treatment with sodium methoxide in dry methanol at ambient temperature afforded the target α-hydroxy-δ-valerolactam **13d** in 76% yield. The three step sequence starting from the amine **10b** gave **13d** in 46% overall yield.

In a second and more efficient, approach (Scheme 2) employing the tandem ring opening-ring closure methodology, acylation of the amine **10b** with the acid chloride **5** in N,N-dimethylacetamide furnished the tetrahydrofuroanilide **14b** in 86% yield. Treatment of **14b** with hydrogen bromide/acetic anhydride[13] afforded the crude α-acetyloxy-ω-bromovaleroyl anilide **15b**, which without isolation was lactamized in the presence of potassium carbonate to obtain the α-acetyloxy-δ-lactam **12b** in 49% isolated yield. Deacetylation of **12b** to obtain **13d** has already been described.

Scheme 2



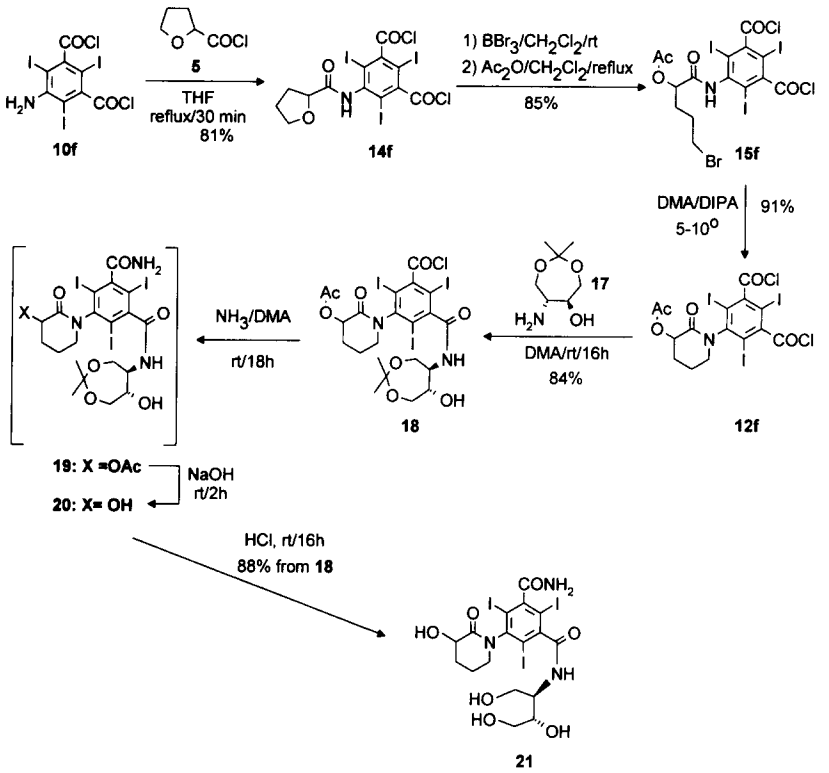
To study the effect of an unprotected hydroxyl group on the course of the base promoted lactamization reaction, we carried out the ether cleavage of **14b** employing dimethylboron bromide in methylene chloride and hydrolyzed the resulting boronic ester by aqueous work-up, to obtain the α-hydroxy-ω-bromovaleroyl anilide **16b** in 92% purity. Similar to the observation of Guindon et al.[8], the ether cleavage of **14b** was chemoselective and the acetate and amide moieties in the molecule were not affected. Compound **16b**, if allowed to stand at room temperature, tended to slowly cyclize back to the tetrahydrofuroyl anilide **14b** by O-selective cyclization. However, when **16b** was treated with potassium carbonate in N,N-dimethylacetamide immediately upon isolation, the nitrogen selective cyclization reaction was favored, providing a 7:2 mixture of **13b** and **14b**. This preference for N-participative cyclization over O-participative cyclization in the presence of base is in full conformity with our earlier results in the iodocyclization study of ω-alkenoyl anilides[1c]. It may also be noted that under non-basic conditions, wherein the O-participative cyclization mode is the preferred pathway, **16b** has two options available, viz., ring closure on the hydroxyl group to provide **14b** or ring closure on the amide-O atom to give a 2-iminotetrahydropyran derivative. In practice only the formation of **14b** is observed under non-basic conditions. This result is probably attributable to the lower rate of cyclization for 6-membered versus 5-membered rings[14]. Deacetylation of **13b** to **13d** was achieved as already described. An unexpected dividend in this approach was the facile conversion of **14b** into the tetrol **14d**, which by itself is of interest as a radiographic agent.

*The unsymmetrically substituted isophthalamide **21**.* A recent report[7] claimed unusually low osmolality when one of the isophthalamide nitrogen atoms in a triiodoisophthalamide was left unsubstituted. To find out whether this observation would be applicable to *5-heterocyclically substituted* congeners as well, the synthesis of the unsymmetrically substituted isophthalamide **21** was undertaken. In the molecule **21** the trihydroxy-butyl side chain was chosen to provide a sufficient number[15] of water solubilizing hydroxyl groups.

It occurred to us that a synthetically convergent approach to unsymmetrically substituted triiodo-iosphthalamides could consist of extending the tandem ring opening-ring cleavage methodology to tetrahydrofuroanilides bearing a triiodo-isophthalic bis-chloride moiety on the nitrogen atom and then sequentially amidate the acid chloride functions, as shown in Scheme 3. Towards this end 5-amino-2,4,6-triiodo-isophthaloyl chloride (**10f**) was treated with **5** in refluxing tetrahydrofuran to obtain the anilide **14f** in 81% yield. The tetrahydrofuroyl ring cleavage and subsequent O-acetylation of **14f** were effected in one pot by treatment, first with 0.5 equivalents of BBr_3, and then with an excess of acetic anhydride in methylene chloride to obtain the α-acetyloxy-δ-bromo-valeroyl anilide **15f**, in 85% yield. Lactamization of **15f** in N,N-dimethylacetamide in the presence of diisopropylamine afforded the α-acetyloxy-δ-valerolactam **12f** in 91%

yield. Treatment of **12f** with 5-amino-2,2-dimethyl-6-hydroxy-dioxepane[16] (**17**) at room temperature for 16 h led to the monoamide **18**, which *in situ* was exposed to ammonia at room temperature for 18 h to obtain the fully protected, unsymmetrically substituted, isophthalamide **19**. The crude compound **19** was deacetylated

Scheme 3

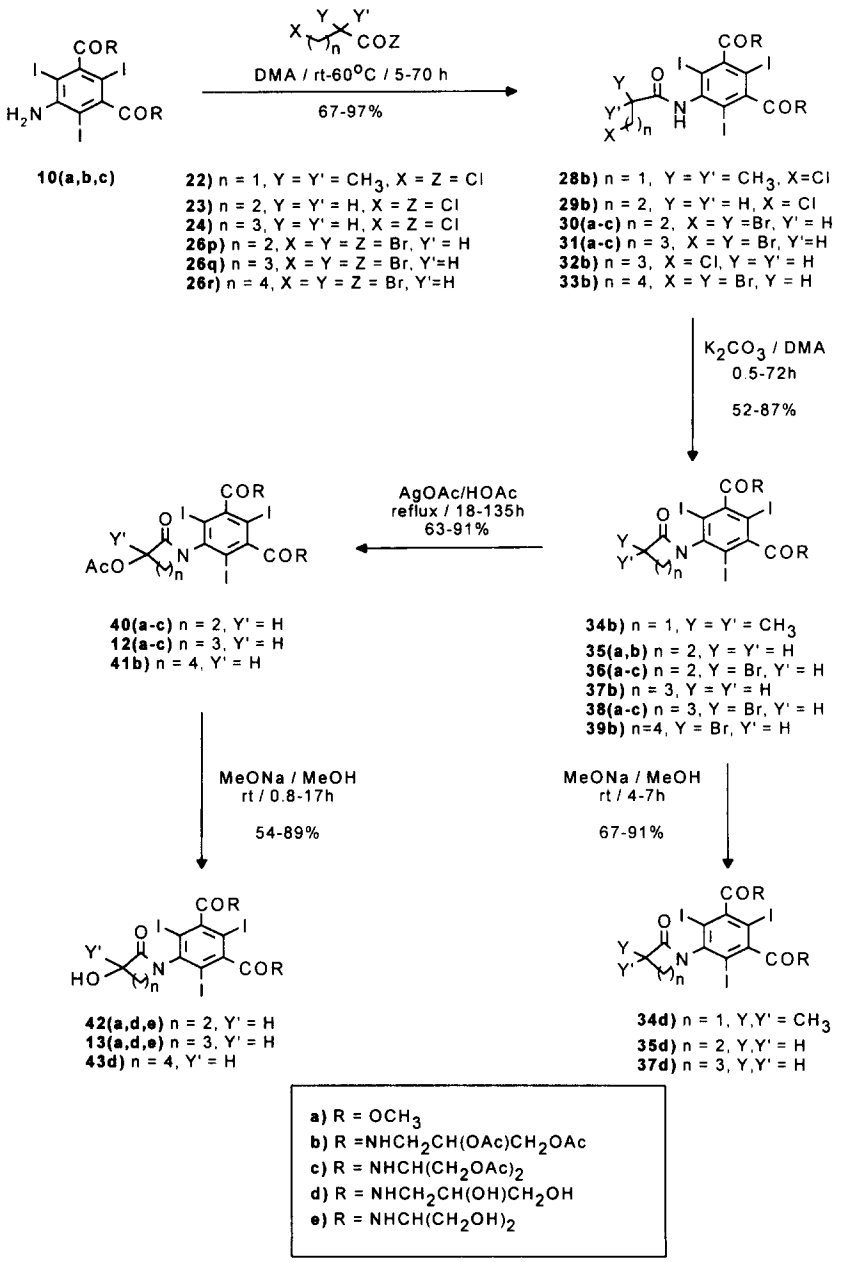


with sodium hydroxide to obtain **20**, which without isolation was hydrolyzed with hydrochloric acid to get the desired compound **21** in 88% overall yield from **18**.

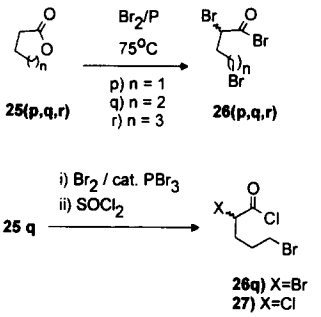
Synthesis of NICM candidates based on lactams of differing ring sizes and substitution patterns

Preliminary evaluation of the target molecules based on the α-hydroxy-δ-valerolactam ring system encouraged us to initiate an effort to synthesize related lactam analogs, in which the ring size and substitution pattern of the lactam moiety will be varied. The objective was to define the optimal substitution pattern that

Scheme 4


DMA / rt-60°C / 5-70 h
67-97%
10(a,b,c)
22) n = 1, Y = Y' = CH3, X = Z = Cl
23) n = 2, Y = Y' = H, X = Z = Cl
24) n = 3, Y = Y' = H, X = Z = Cl
26p) n = 2, X = Y = Z = Br, Y' = H
26q) n = 3, X = Y = Z = Br, Y'=H
26r) n = 4, X = Y = Z = Br, Y'=H
28b) n = 1, Y = Y' = CH3, X=Cl
29b) n = 2, Y = Y' = H, X = Cl
30(a-c) n = 2, X = Y =Br, Y' = H
31(a-c) n = 3, X = Y = Br, Y'=H
32b) n = 3, X = Cl, Y = Y' = H
33b) n = 4, X = Y = Br, Y = H
K2CO3 / DMA
0.5-72h
52-87%
AgOAc/HOAc
reflux / 18-135h
63-91%
40(a-c) n = 2, Y' = H
12(a-c) n = 3, Y' = H
41b) n = 4, Y' = H
34b) n = 1, Y = Y' = CH3
35(a,b) n = 2, Y = Y' = H
36(a-c) n = 2, Y = Br, Y' = H
37b) n = 3, Y = Y' = H
38(a-c) n = 3, Y = Br, Y' = H
39b) n=4, Y = Br, Y' = H
MeONa / MeOH
rt / 0.8-17h
54-89%
MeONa / MeOH
rt / 4-7h
67-91%
42(a,d,e) n = 2, Y' = H
13(a,d,e) n = 3, Y' = H
43d) n = 4, Y' = H
34d) n = 1, Y,Y' = CH3
35d) n = 2, Y,Y' = H
37d) n = 3, Y,Y' = H
a) R = OCH3
b) R =NHCH2CH(OAc)CH2OAc
c) R = NHCH(CH2OAc)2
d) R = NHCH2CH(OH)CH2OH
e) R = NHCH(CH2OH)2

Scheme 5



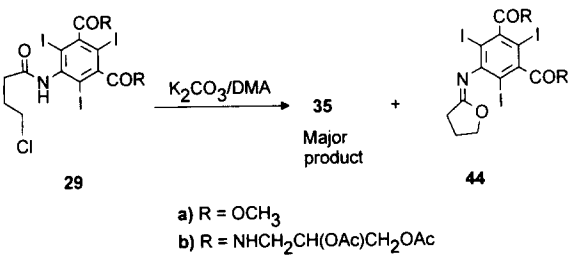
will strike a balance between high biological tolerance expected from hydrophilic substitution and low osmolality expected from hydrophobic substitution on the lactam ring. We also included in this study an extension of the general lactam synthesis approach for the preparation of the α-hydroxy-valerolactams reported above, in view of their special interest as preferred candidates for further development as radiographic contrast agents.

The synthetic route employed for the lactams **13**, **34**, **35**, **37**, **42**, and **43** is shown in Scheme 4. While the acid chlorides **22**, **23**, and **24** were commercially available, we attempted to prepare **26q** (Scheme 5) by treating **25q** first with bromine in the presence of phosphorus tribromide, and then with thionyl chloride at reflux, as described[17a]. However, we obtained only a mixture of **26q** and **27**. The presence of **27** was undesirable since the α-chloro substituted products that resulted from it downstream proved to be resistant to the desired nucleophilic displacement reaction. In light of this, we treated[17b] the lactones **25(p-r)** with red phosphorus and bromine at room temperature and then with an additional equivalent of bromine at 75°C to obtain the acyl bromides **26 (p-r)** in 68, 55, and 78 % yields, respectively.

Acylation of anilines. The required anilides **28-33** were prepared in good yields by treatment of the dimethyl ester **10a**[1c] or the bis amides **10(b,c)**[1c] with the appropriate acid halide **22**, **23**, **24**, or **26(p-r)** in N,N-dimethylacetamide, usually at ambient temperature, with the exception of the anilide **28b** which required a reaction temperature of 60°C for 70h. Generally the ω-haloanilides were isolated and characterized, with the exception of **29a**, which was subjected to cyclization without isolation, and **30(a-c)**, which could not be isolated in the pure form due to partial cyclization to the γ-lactams during workup and purification.

Conversion of the anilides into the protected lactams. As a model study, the base promoted cyclization of the ω-haloanilides belonging to the dimethyl ester series was initially studied. The crude ω- chloro-

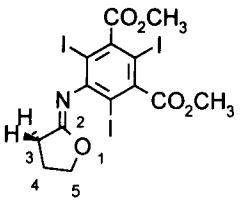
Scheme 6



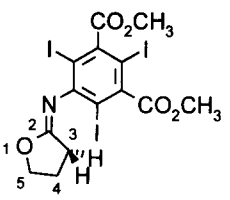
butyranilide **29a**, when treated with potassium carbonate in N,N-dimethylacetamide at room temperature for 3 days, furnished the desired γ-lactam **35a** in 72% yield, along with the amide oxygen cyclization product **44a** in 7% yield (Scheme 6). In the ^{13}C-NMR spectra the C-5 carbon atom of the iminotetrahydrofuran ring in **44a** occurred at 71.9 ppm, whereas the corresponding carbon atom in the lactam **35a** was at 47.2 ppm providing strong evidence. This was confirmed by the ^{1}H-NMR spectra, the heterocyclic C-5 methylene protons in **44a** and **35a** occurring at 4.36 ppm and 3.72 ppm, respectively.

Further examination of the NMR data revealed interesting features indicative of the existence of **44a** as a mixture of *syn-anti* isomers. Whereas the integral values of the peaks at 2.55(2H), 2.30(2H), and 3.72(2H) ppm, assignable to the methylene protons on the lactam carbon atoms 3, 4, and 5 in **35a**, were equal, the corresponding methylene protons in the iminotetrahydrofuran **44a** at 2.81(1.5H), 2.20(2.4H), and 4.36(2.1 H) displayed unequal integral values. The lower than expected integral for the C-3 protons and the higher integral for the C-4 protons point to the existence of the iminotetrahydrofuran ring as a ~3:1 mixture, based on the observed integral values for the peaks at 2.20 and 2.81 ppm of the *anti* and *syn* isomers about the imine bond (Figure 1). This is reminiscent of our earlier observations in the case of the iodomethyl substituted iminotetrahydrofurans, formed during the iodocyclization of ω-alkenylanilides[1d]. The anomalous integral values observed can be explained by postulating that the resonance due to the C-3 methylene protons in the *anti*-**44a** isomer is at 2.81 ppm, whereas that due to the same protons in the *syn*-**44a** isomer, coming under the influence of the diamagnetic shielding effect of the aromatic ring, is at 2.20 ppm, accidentally coincident with the resonance due to the C-4 methylene protons. The ^{13}C-NMR spectrum also provided evidence for the presence of both ***syn*-44a** and ***anti*-44a**. The heterocyclic C3 carbon is represented by two resonances at 27.8

Figure 1. Iminotetrahydrofuran anti-44a and syn-44a



***anti* - 44a**



***syn* - 44a**

and 28.9 ppm, the former resonance being the smaller and assignable to ***syn*-44a** and the latter to ***anti*-44a**, based on the trends in the chemical shift for the C3 carbon atom of ***syn*** (25.0 ppm) and ***anti*** (29.8 ppm) N-phenyl-2-iminotetrahydrofuran[18].

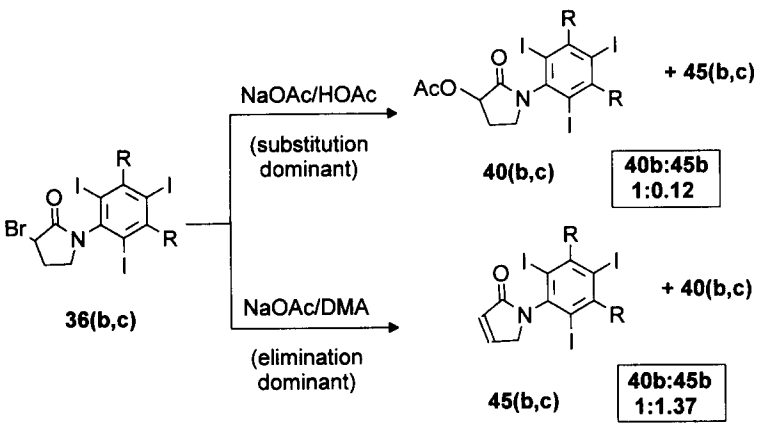
Treatment of the bis-methyl esters **30a** and **31a** with potassium carbonate in N,N-dimethylacetamide at room temperature afforded the bromolactams **36a** and **38a**, respectively, in 52% and 73% yields. However, no effort was made to isolate the iminotetrahydrofuran side products that may have been formed. In the isophthalamide series, the anilides **28b**, **29b**, **31b**, **31c**, **32b**, and **33b** afforded the corresponding lactams **34b**, **35b**, **38b**, **38c**, **37b**, and **39b**, in 72 - 87% yields, when similarly treated. Of note is the facile ring closure of **28b** to give the β-lactam **34b** in high yield, undoubtedly arising from the Thorpe-Ingold effect[19]. The anilides **30b** and **30c**, which could not be isolated in pure form, were cyclized in the crude state to obtain the γ-lactams **36b** and **36c**, in 57% and 75% yields, respectively. The NMR spectral properties of the heterocyclic ring protons of the lactams were very similar to those of the lactams **35a** and **38a** in the methyl ester series. However additional features characterized the NMR spectra of the lactams derived from 1,3-benzenedicarboxamides, arising in general, from the presence of atropoisomerism and geometrical isomerism in triiodo-isophthalamides[20] and, in the particular case of those bearing the aminopropane-2,3-diol side chain, from their being a mixture of diastereomers.

As a representative example of isophthalamides, the products formed during the cyclization of the anilide **29b** were carefully analyzed. In addition to the desired lactam **35b**, the formation of the iminotetrahydrofuran **44b** in 5% yield, by amide oxygen participative cyclization, was noticed. Compound **44b** was unambiguously characterized by analytical and NMR spectral data, which indicated that, as in the case of **44a**, **44b** was also present as a mixture of *syn* and *anti* isomeric forms. It is assumed that such side products are formed in all the lactamization reactions of isophthalamides, though no effort was made to isolate and characterize them. However, in view of the potential of the iminotetrahydrofurans **44** to undergo

hydrolysis to the much more toxic parent amines **10**, we paid special attention to the purification of the desired lactams.

Conversion of the α-bromolactams into the α-acetyloxylactams. In the bis-methyl ester series, the conversion of the bromo-lactams **36a** and **38a** into the acetyloxy-lactams **40a** and **12a** was readily achieved by refluxing with a large excess of silver acetate in acetic acid for 24 h in 91% and 71% yields, respectively. In the isophthalamide series, similar treatment of the bromo-lactam **38b** afforded the acetyloxylactam **12b**, in 74% yield, identical with the compound obtained earlier by the tandem ring opening- ring closure methodology (see Schemes 1 and 2). In an analogous fashion, the bromolactams **36b**, **36c**, **38c**, and **39b** were converted into the corresponding acetyloxy-lactams **40b**, **40c**, **12c**, and **41b**, in 63 - 74% yields. In the case of **36b** and **36c**, careful HPLC analysis of the crude product mixtures revealed that, in addition to the desired α-acetyloxy-lactams **40b** and **40c** (~97%), more polar side products resulted, albeit in very low yields (~2%). These side products were identified to be the corresponding elimination products **45b** and **45c** (Scheme 7), based on NMR data. In the case of **45c**, for instance, the vinyl protons at positions 3 and 4 of the heterocycle

Scheme 7



appeared at 6.23 and 7.26 ppm, respectively. The ^{13}C-NMR spectrum displayed resonances for the lactam ring C3 and C4 sp^2 carbons at 127 ppm and 146 ppm, entirely consistent with the assigned structure.

In the case of the bis amide **36b**, use of systems such as sodium acetate/N,N-dimethylacetamide or sodium acetate/acetic acid to effect the above displacement led to substantial amounts of **45b**, the ratio of elimination to substitution being 1.37 or 0.12, respectively. As expected the change from N,N-dimethylacetamide to acetic acid in this reaction reduced elimination significantly. However in view of the propensity for greater elimination with sodium acetate, these approaches were not pursued further.

Conversion of the acetyloxylactams into the hydroxylactams. In the bis-methyl ester series, the α-acetyloxy-lactams **40a** and **12a** were next converted into the corresponding hydroxy-lactams **42a** and **13a** in 61% and 76 % yields, respectively, by treatment with sodium methoxide in dry methanol at ambient temperature. In the isophthalamide series, similar deblocking of the side chain and/or the lactam α-acetate functions in compound **12b** to obtain **13d** has already been described (see Schemes 1 and 2). In an analogous manner, deacetylation of lactams **34b**, **35b**, **37b**, **40a**, **40b**, **40c**, **12a**, **12c**, and **41b**, led to the NICM candidates **34d**, **35d**, **37d**, **42a**, **42d**, **42e**, **13a**, **13e**, and **43d** in excellent yields. Noteworthy is the β-lactam ring of **34d**, which did not suffer any cleavage, due obviously to steric hindrance afforded by the iodine atoms and α,α-dimethyl substitution.

Purification of the target candidates

Final purification of the NICM candidates in the isophthalamide series was achieved using low pressure reversed phase column chromatography employing the Diaion CHP-20P resin[1c]. The target NICM were obtained in 70-89% yield and >99 % purity and all analytical and spectral data were in complete agreement with the structures assigned. In the ^{13}C-NMR spectrum, the iodine-bearing C-4 and C-6 carbons of the aromatic ring appeared as a cluster of at least four peaks at 97-99 ppm. Comparison of the ^{13}C-NMR spectrum of the γ-lactam **35d** with that of **42d** clearly shows the effect of lactam α-hydroxy substitution on the chemical shift difference between the aromatic ring C-4 and C-6 resonances. In compound **35d,** where there is no α-substitution, these resonances are separated by only 0.08 ppm, whereas in compound **42d**, wherein an α-hydroxy group is present on the lactam ring, the separation is 1.46 ppm. In the unsubstituted δ-lactam compound **37d** the separation is 0.65 ppm, whereas in the α-hydroxy substituted δ-lactam **13d** the separation is noticeably larger (>1 ppm). These differences are reflective of the asymmetry introduced in the molecule by the chiral center.

Evaluation of the New NICM Candidate Compounds

A standard test for hydrolytic stability of NICM is heating an aqueous solution at 100 °C for up to 72 h and assessment of the rate of decomposition. All of the compounds reported in this study showed less than 0.4

% decomposition over periods of 24-72 h, Iopamidol (**1**) showing 1.3% decomposition[1a]. All of the symmetrically substituted compounds bearing the 2,3-dihydroxypropyl substitution were water soluble providing stable solutions at a concentration of 0.97 M (~80% w/v of the NICM). Compounds having the 1,3-dihydroxypropyl substitution displayed variable results. Compound **42e** was water soluble, whereas the 6-membered analog **13e** was only sparingly soluble. The osmolality[6] of aqueous solutions of the symmetrically disubstituted NICM candidates were 8-30% lower then that of **1**. A good linear correlation between the osmolality at 1.05 M concentration and HPLC log k' values, which are a measure of hydrophobicity, was also observed, the hydrophobicity parameter and osmolality being inversely proportional to each other. We thus verified our hypothesis that rigidification by heterocyclization and increase in hydrophobicity by the deletion of hydrophilic functionalities might lead to increased self association and thereby to lowered osmolality in aqueous solution. We further observed that the primary amide **21** was highly water soluble and that at 1.0 M concentration was isotonic with plasma, reflecting a lowering of osmolality by ~50% compared to **1**. Thus lowering symmetry seems to be an effective strategy for maintaining water solubility, while lowering osmolality.

We had earlier[1a-b] reported on the anticoagulant property of the heterocyclic NICM. Similarly, the new NICM candidates, synthesized in this study, were also generally better anticoagulants than nonionic NICM, such as **1** and **2**. Some of the new candidates, viz. **34d**, **35d**, **37d**, and **43d**, were even better in this regard than the ionic contrast agent diatrizoic acid (**3**), which is a known[21] anticoagulant.

Summary and Conclusions

We have synthesized several sterically congested lactams bearing the 2,4,6-triiodoisophthalamide group as X-ray contrast agents. A tandem ring opening - ring closure methodology was used to convert tetrahydrofuranilides such as **14b** into α-O-functionalized-δ-valerolactams **12b** or **13b**. Deacetylation furnished the desired candidate **13d**. The study was extended to make a series of lactams of varying ring sizes and substitution patterns by employing an amide nitrogen-selective intramolecular cyclization of ω-haloalkyl anilides, exemplified by the conversion of **28**, **29**, **30**, **31**, **32** and **33**, into the lactams **34**, **35**, **36**, **37**, **38**, and **39**. The α-bromo-lactams **36**, **38**, and **39** were converted into the corresponding α-hydroxy lactams **42**, **13**, and **43** by Ag^+ ion assisted acetolysis, followed by deacetylation. The unsymmetrically substituted isophthalamide **21** was prepared in an effort to explore the effect of side chain variation on osmolality. Its isotonicity with respect to plasma indicated that primary carboxamide substituted NICM candidates could be an important class of NICM. Several of the target compounds were highly water soluble. They were also more stable to hydrolysis and had lower osmolality than currently employed NICM. A unique anti-coagulant

effect exhibited by some of these heterocyclically substituted compounds may render them especially useful for invasive procedures, wherein the lowered anticlotting property of currently used NICM is of concern.

EXPERIMENTAL

General Methods and Materials

Melting points are uncorrected. The acid chlorides **22**, **23**, and **24** were procured from Aldrich Chemical Co. Inc. The 5-amino-2,4,6-triiodo-1,3-benzenedicarboxylic derivatives **10** were prepared[1c] as described earlier. Infrared spectra were obtained on potassium bromide pellets unless otherwise stated. ^{1}H-NMR and ^{13}C-NMR data are at 270 and 68 MHz, respectively, in deuteriochloroform unless otherwise stated. All assignments made in the ^{13}C-NMR spectra were verified by INEPT experiments. Flash column chromatography was carried out over silica gel. HPLC analyses were carried out, unless otherwise specified, with a reverse phase C8-silica column (15 cm x 4.6 mm i.d.) using acetonitrile/water at a flow rate of 0.5 mL /min, and the UV detector set at 254 nm. The extent of hydration of the new compounds was determined by the desorption or by the dissolution K-F titration method.

Procedure A-1 for the acylation of the amines 10a-c employing acid chlorides. To a stirred solution (0.3 - 0.5 M) of the amine **10** in N,N-dimethylacetamide under a nitrogen atmosphere was added the acid chloride **22**, **23** or **24** (1.4 - 6.0 equivalents) dropwise at room temperature and the mixture stirred at room temperature until the reaction was completed. The volatiles were removed and a solution of the residue in ethyl acetate was washed with aqueous sodium bicarbonate and then with water. The organic layer was dried and solvent removal furnished the crude product, which was purified by chromatography or by crystallization to obtain the pure anilides. In the case of **29a** and unstable **30(a-c)** the crude anilides were directly taken to the next cyclization step.

Procedure A-2 for the acylation of the amines 10a-c employing acid bromides. The procedure was the same as for procedure A-1 except that the acid bromide was added at 0°C, the reaction mixture stirred at 0°C for 1 h, and then at room temperature until the reaction was completed.

Procedure B for cyclization to lactams. To a stirred solution of the anilide **28-33** in N,N-dimethylacetamide finely powdered potassium carbonate was added and the mixture stirred at room temperature until the reaction was completed. Mode of workup and purification depended on the solubility and polarity characteristics of the resulting crude lactam and are described below for each compound.

Procedure C for the conversion of α-bromolactams into α-acetyloxylactams. To a solution of the α-bromolactam **36**, **38** or **39** in acetic acid under nitrogen excess silver acetate (4-5 equivalents) was added and the mixture heated to reflux until the reaction was completed. The insoluble salts were filtered off, acetic acid removed *in vacuo*, and the residue partitioned between ethyl acetate and brine. The aqueous layer was extracted with ethyl acetate and the combined organic layers washed with water, brine, and dried. Solvent removal provided the crude product, which was purified by chromatography or by crystallization, to obtain the pure α-acetyloxylactam.

Procedure D for deacetylation. To a solution of the acetylated derivative **12**, **34**, **35**, **37**, **40**, or **41** in dry methanol was added a solution of sodium methoxide in methanol and the solution stirred at room temperature until the reaction was completed. The solution was then neutralized by the addition of AG-50X8-H^+ resin. The resin was filtered off and the solvent removed. The residue was purified by crystallization or by chromatography over Diaion CHP-20P resin. For the latter, an aqueous solution of the crude product was applied to the column, which was then washed with water with monitoring of the eluent with a conductivity meter. After the salts were eluted off, the column was eluted batchwise with a stepwise gradient from water to 5-20% aqueous ethanol and the eluent monitored using a UV detector at 254 nm. The fractions containing the pure product were combined and the solvent removed *in vacuo* to obtain the pure hydroxylactam.

Tetrahydrofuran-2-carbonyl chloride (5). A mixture of **4** (2.32 g, 20 mmole) and oxalyl chloride (6.36 g, 50 mmole) was stirred at room temperature for 15 h. The volatiles were removed and the residue distilled *in vacuo* to obtain pure **5** (2.42 g, yield 90%) as a colorless liquid. bp: 75-76°C, 23 mm Hg; (lit.[10] 95-100°C, 33 mm. Hg). gc: (as the methyl ester): t_R 6.5 min, purity >99% on a 6' x 10% OV 101 on Chromosorb WHP column; temperature gradient 50-180°C at 10°C/min; Injection port, 180°C; FID detector. ^{1}H-nmr: δ 1.93-2.04 (m, 2H); 2.17-2.29 (m, 1H), 2.29-2.46 (m, 1H); 3.94-4.08 (m, 2H), 4.73 (dd, J_1 = 8.58 Hz, J_2= 5.28 Hz, 1H). ^{13}C-nmr: δ 24.6, 29.9, 70.0, 83.9, 175.2.

Benzyl tetrahydrofuran-2-carboxylate (6). To a cold solution of benzyl alcohol (10.9 g, 0.1 mole) in dry ether (200 mL) and pyridine (20.0 g, 0.25 mole) **5** (15.0 g, 0.11 mole) was added dropwise and the solution stirred at 0°C for 40 min. The mixture was filtered and the filtrate washed with 0.1 M hydrochloric acid (50 mL), aqueous sodium bicarbonate (50 mL), and dried. Evaporation and distillation *in vacuo* provided **6** as a colorless oil (21.1 g, 100% yield). bp: 118 -120°C, 0.5 mm Hg. gc: t_R 15.7 min, purity 95% on a 6' x

1/8'' column of 10% OV 101; injection temperature 180°C; column temperature 50-180°C at 10°C/min. ir: 2953, 1750, 1273, 1194, 1173, 1088 cm^{-1}. ^{1}H-nmr: δ 1.9-2.3 (m, 4H), 4.1 (m, 2H), 4.5 (m, 1H), 5.3 (s, 2H), 7.4 (m, 5H). ^{13}C nmr: δ 24.9, 29.9, 66.1, 69.0, 76.4, 127.9, 128.0, 128.1, 128.3, 135.4, 172.9. ms: m/z 224 $(M+NH_4)^+$. Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84; O, 23.27. Found: C, 69.62; H, 6.89.

Benzyl 2-acetyloxy-5-chloropentanoate (7). To a suspension of freshly fused zinc chloride (35 mg, 0.25 mmole) in acetyl chloride (31 mL, 436 mmole), **6** (15 g, 72 mmole) was added dropwise and the mixture heated to reflux with stirring for 17 h. The volatiles were removed and a solution of the residue in ether (200 mL) was washed with aqueous sodium bicarbonate (50 mL) and dried. Solvent removal, chromatography using 20% ethyl acetate in heptane, and distillation *in vacuo* furnished **7** as a yellow oil (17.6 g, 85% yield), which crystallized upon refrigeration for several days. bp: 144-152°C, 0.1 mm Hg. mp: 40-41°C. tlc: R_f 0.34 in ethyl acetate-heptane, 1:4. gc: t_R 19.1 min, purity 99.1% on 6' X 1/8" column of OV 101 liquid phase; injection temperature 180°C; column temperature 50-180°C at 20°C/min. ir (neat): 1746, 1236 cm^{-1}. ^{1}H-nmr: δ 1.8-2.2 (m, 4H), 2.2 (s, 3H), 3.6 (t, J= 6.0 Hz, 2H), 5.2 (dd, J_1 =5.3 Hz, J_2 =6.6 Hz, 1H), 5.3 (AB quartet, J_{ab}= 12.5 Hz, δ_{ab} = 7.0 Hz, 2H), 7.4 (m, 5H). ^{13}C nmr: δ 20.5, 27.9, 28.3, 44.0, 67.0, 71.4, 128.1, 128.3, 128.1, 128.5, 135.0, 169.5, 170.2. ms: m/z 304, 302 $(M+NH_4)$ (3:1 chlorine isotope ratio), 224, 176, 168, 108. Anal. : Calcd. for $C_{14}H_{17}O_4Cl$: C, 59.06; H, 6.02; Cl, 12.45; O, 22.48. Found: C, 59.22; H, 6.04; Cl, 12.63.

2-(Acetyloxy)-5-chloropentanoic acid (8). A solution of **7** (15.3 g, 53.7 mmole) in ethyl acetate (170 mL) and acetic acid (9.0 mL) was hydrogenated in the presence of 5% Pd/C (0.96 g) at 10 psi for 1 h. Filtration (Celite), solvent removal, and distillation *in vacuo* gave compound **8** as a colorless liquid (9.1g, 87% yield). bp: 135-136°C, 0.03 mm Hg. gc: (as the methyl ester) t_R 6.6 min, purity 100 % on a 6' X 1/8" column of OV 101 liquid phase; injection temperature 180°C; column temperature 50-180°C at 20°C/min. ir (neat): 2967, 1744, 1235 cm^{-1}. ^{1}H-nmr: δ 1.9-2.1 (m, 4H), 2.2 (s, 3H), 3.6 (t, J= 6.2 Hz, 2H), 5.1 (m, 1H), 9.4 (bs, 1H). ^{13}C nmr: δ 20.4, 27.9, 28.1, 44.0, 71.1, 170.8, 174. ms: m/z 214, 212 $(M+NH_4)^+$ (chlorine isotopic ratio 3:1). Anal. Calcd. for $C_7H_{11}O_4Cl$: C, 43.20; H, 5.70; Cl, 18.22; O, 32.88. Found: C, 42.95; H, 5.80; Cl, 17.84.

2-(Acetyloxy)-5-chloropentanoyl chloride (9). A mixture of **8** (7.99 g, 41.1 mmole) and oxalyl chloride (13.1 g, 0.1 mole) was stirred at 25°C for 15 h. The volatiles were removed and the residue distilled *in vacuo* to obtain **9** as a colorless liquid (8.51 g, 97% yield). bp: 76-78°C, 0.5 mm Hg. gc: (as the methyl ester prepared by reaction of the acid chloride with methanol): t_R 6.6 min, purity 100% on a 6' X 1/8" column using OV 101 as the liquid phase; injection temperature 180°C; column temperature 50-180°C at 20°C/min.

^{1}H-nmr: δ 1.9-2.1 (m, 4H), 2.1 (s, 3H), 3.5 (t, J=6.3 Hz, 2H), 5.1 (dd, J_1 = 4.6 Hz, J_2=7.3 Hz, 1H). ^{13}C-nmr: δ 20.2, 27.5, 27.6, 43.7, 77.7, 169.8, 171.9. ms: m/z 234, 232, 230 $(M+NH_4)^+$ (9:6:1 ratio for isotope peaks representing two chlorine atoms). Anal. Calcd. for $C_7H_{10}O_3Cl_2$: C, 39.46; H, 4.73; Cl, 22.53; O, 33.28. Found: C, 39.78; H, 4.79.

5-[[2-(Acetyloxy)-5-chloro-1-oxopentyl]-amino]-N,N'-bis[2,3-bis(acetyloxy)-1-propyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (11b). Starting from **10b** (8.73 g, 10 mmole), N,N-dimethylacetamide (400 mL), and **9** (3.7 g, 17 mmole) and employing procedure A-1 for 15 h, **11b** (8.31 g, 79% yield) was obtained as a white solid, after chromatography using ethyl acetate-heptane (7:3). tlc: *Rf* 0.48 in ethyl acetate. hplc: t_R 14.2 min (purity 99.3%) in acetonitrile-water (2:3) at 1.0 mL/min. ir: 3291, 1740, 1663, 1545, 1223 cm^{-1} ^{1}H-nmr (dimethylsulfoxide-d_6): δ 2.0-2.3 (m, 4H), 2.1 (s, 12H), 2.2 (s, 3H), 3.3-3.7 (m, 4H), 3.8 (t, J=6.6 Hz, 2H), 4.2-4.5 (m, 4H), 5.20 (bs, 2H), 5.4 (bs, 1H), 8.5-9.1(m, 2H, exchangeable with deuterium oxide), 10 .2 (s, 1H, exchangeable with deuterium oxide). ^{13}C-nmr (dimethylsulfoxide-d_6): δ 20.6, 20.8, 28.1, 28.7, 38.6, 44.9, 63.0, 69.5, 72.2, 90.0, 98.5, 99.5, 142.3, 149.9, 150.0, 167.2, 167.3, 169.6, 169.7, 169.9, 170.2. . ms (FAB): m/z 1052, 1050 $(M+H)^+$ (3:1 ratio for chlorine isotope cluster), 1008, 990, 924, 747. Anal. Calcd. for $C_{29}H_{35}N_3O_{13}I_3Cl$.•0.25 H_2O: C, 33.04; H, 3.39; N, 3.99; I, 36.11; Cl, 3.36; O, 20.11. Found: C, 33.39; H, 3.08; N, 3.70; I, 35.65; Cl, 3.32; H_2O (KF) 0.43% (0.25 mole).

Dimethyl 5-[3-(acetyloxy)-2-oxo-1-piperidinyl]-2,4,6-triiodo-1,3-benzenedicarboxylate (12a). Starting from **38a** (0.48 g, 0.64 mmole), silver acetate (0.75 g, 4.5 mmole), and acetic acid (15 mL) and employing procedure C for 21 h, **12a** (0.33 g, yield 71%) was obtained as a crystalline solid from ethyl acetate. mp: 248-50°C. tlc: *Rf* 0.36 in ethyl acetate-hexane (1:1). hplc: t_R 5.51 min in acetonitrile-water (7:3) at 0.5 mL/min. uv: (acetonitrile): λ_{max} 241 nm (ε 30,790). ir: 1733, 1681; 1532, 1232 cm^{-1}. ^{1}H-nmr (dimethylsulfoxide-d_6) δ 2.02-2.20 (m, 4H); 2.09 (s, 3H), 3.42 and 3.58 (2m, 2H), 3.91 (s, 6H), 5.34 (dd, 1H, J1 = 4.98 Hz, J2 = 4.98 Hz). ^{13}C-nmr (dimethylsulfoxide -d_6) δ 19.9, 20.6, 26.3, 48.1, 53.3, 68.5, 89.6, 146.9, 148.1, 165.2, 167.8, 169.2. ms: m/z 727.7 (MH^+), 685.6, 599.9. Anal. Calcd. for $C_{17}H_{16}I_3NO_7$•0.02 H_2O : C, 28.07; H, 2.22; I, 52.35; N, 1.93; O, 15.40. Found: C, 28.16; H, 1.92; I, 52.00; N, 1.77. H_2O (KF) 0.04 % (0.02 mole).

5-[3-(Acetyloxy)-2-oxo-1-piperidinyl]-N,N'-bis[2,3-bis(acetyloxy)propyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (12b). Method I: From 11b: Starting from **11b** (6.00 g, 57.1 mmole), N,N-dimethylacetamide (29 mL), and potassium carbonate (3.32 g, 24 mmole) and employing procedure B for 24 h, workup as for **35b**, and purification by chromatography using ethyl acetate-heptane (4:1) **12b** (4.56 g, 79%

yield) was obtained as a white solid. TLC *Rf* 0.65 in ethyl acetate. hplc: t_R, 5.17 min by 10 cm column in acetonitrile-water(1:1) at 0.5 mL/min. uv (acetonitrile): λ_{max} 241 nm (ε 29,600). ir: 1740, 1672, 1545, 1238 cm^{-1}. ^{1}H-nmr (dimethylsulfoxide -d_6): δ : 2.03 (s, 12 H, singlet), 2.08 (s, 3H), 1.97-2.26 (m, 4H), 3.34- 3.57 (m, 6H), 4.21 (dd, 2H), 4.28 (dd, 2 H), 5.09 (m, 2H), 5.30 (m, 1 H), 8.74 and 9.93 (d, 2H). ^{13}C-nmr (dimethylsulfoxide -d_6): δ 18.6, 20.9, 21.31, 27.4, 38.1, 48.6, 63.5, 68.9, 69.8, 92.3, 97.1, 146.6, 150.8, 165.2, 169.7, 169.8 and 170.5. ms: m/z 1014 (MH^+), 972, 954, 912, 886, 870, 839, 826, 797, 784, 768, 713, 700, 642, 557, 515. Anal. Calcd. for $C_{29}H_{34}I_3N_3O_{13}$ •1.01 H_2O : C, 33.77; H, 3.52; I, 36.91; N, 4.07; O, 21.73. Found: C, 33.86; H, 3.17; I, 37.15; N, 3.91; H_2O (KF) 1.76% (1.01 mole).

Method II: from 14b: A mixture of **14b** (0.194 g, 0.2 mmole), ethyl acetate (5 mL), and the hydrogen bromide-acetic anhydride reagent (3 mL, prepared by passing hydrogen bromide gas through acetic anhydride at 0-5°C for 2h) was stirred at 5°C for 2 h and then at ambient temperature for 75 h. Nitrogen gas was bubbled for 15 min, the solvent removed *in vacuo* at 40°C and the residue dissolved in ethyl acetate (50 mL) and washed with water, cold aqueous sodium bicarbonate, water, and brine. Drying and solvent removal *in vacuo* gave **15b** (0.22 g), which was treated with potassium carbonate (0.3 g) in N,N-dimethylacetamide (5 mL) following procedure B for 15 h. The mixture was filtered, the filtrate concentrated *in vacuo*, and the residue purified by chromatography using hexane-ethyl acetate to obtain **12b** (0.1 g, yield 49%) as a white solid, identical with the sample of **Method I**.

Method III: From 38b: Starting from **38b** (66.5 g, 64.3 mmole), silver acetate (32.1 g, 0.19 mole), acetic acid (640 mL), and acetic anhydride (6.6 g, 64.3 mmole) and employing procedure C for 21 h, **12b** (48.77 g, yield 74%) was obtained as an off-white solid, after chromatography using a stepwise gradient from 80-100% ethyl acetate in hexane, identical to the sample prepared by **Method I**.

N,N'-bis[2-(Acetyloxy)-1-[(acetyloxy)methyl]ethyl]-5-[3-(acetyloxy)-2-oxo-1-piperidinyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (12c). Starting from **38c** (22.4 g, 21.7 mmole), silver acetate (12.5 g, 74.8 mmole) and acetic acid (400 mL) and employing procedure C for 28 h, **12c** (15.45 g, yield 70%) was obtained as a white fluffy solid, after crystallization from ethyl acetate. mp: 223-226 °C. tlc: *Rf* 0.23 in ethyl acetate-hexane (8:2). hplc: t_R 5.0 min in acetonitrile-water (1:1) at 0.5 mL/min. uv (acetonitrile): λ_{max} 241 nm (ε = 29,600). ir: 1720, 1635, 1463, 1392, 1227 cm^{-1}. ^{1}H-nmr (dimethylsulfoxide-d_6): δ 1.98-2.19 (m, 4H); 2.04 (s, 12H); 2.09 (s, 3H), 3.35-3.59 (m, 2H), 4.16 (br d, 8H, J=5.3 Hz), 4.34 (m, 2H), 5.31 (dd, 1H), 8.80 and 8.97(2 dd, 1:9 ratio, 2H, J=6.8). ^{13}C-nmr (dimethylsulfoxide -d_6): δ 20.0, 20.7, 26.3, 46.96, 47.05, 62.0, 68.6, 91.1, 97.1, 97.5, 146.3, 150.1, 164.8, 168.9, 169.3, 170.2. ms: m/z 1014 (MH^+), 972, 954, 888, 839, 826.

Anal. Calculated for $C_{29}H_{34}I_3N_3O_{13}$•0.59 H_2O. C,34.01; H,3.46; I, 37.18; N, 4.10; O,21.24. Found: C, 33.94; H, 3.16; I, 37.61; N, 3.95. H_2O, 1.04% (0.59 mole).

2,4,6-triiodo-5-[(3-acetyloxy)-2-oxo-1-piperidinyl]-1,3-benzenedicarbonyl chloride (12f). To a cooled solution of **15f** (100 g, 0.13 mole) in N,N-dimethylacetamide (200 mL) was added diisopropylamine (14.9 g, 0.147 mole) under nitrogen with stirring maintaining the temperature at 5 to 10°C. and the mixture stirred for 3 h. Tetrahydrofuran (200 mL) was added followed by water (200 mL) at a rate to keep the mixture below 30-35°C. The product crystallized out. The mixture was cooled to 5 to 10°C, filtered, washed with aqueous tetrahydrofuran and dried to obtain **12f** as a colorless solid (82.3 g, yield 91%). hplc: t_R 14.1 min by Chromegabond MC-18-3 column 4.6 x 100 mm, 3 μ, in acetonitrile-0.03 M dibasic potassium phosphate (50:50), pH 3.0, at 1 mL/min, detection at 245 nm. ir: 2945, 2915, 1790, 1740, 1670, 1356, 1235, 1001 cm^{-1}. ^{1}H-nmr (300 MHz, dimethylsulfoxide-d_6): δ 1.80-2.40 (m, 7H), 3.20-3.80 (m, 2H), 5.25-5.40 (m, 1H). ^{13}C-nmr (300 MHz, dimethylsulfoxide-d_6): δ 20.15, 20.91, 26.47, 48.39, 68.73, 89.61, 97.21, 97.56, 100.60, 146.38, 149.76, 149.79, 165.28, 169.42, 169.50, 169.56. ms (FAB): 736 $(M+H)^+$,613, 580, 460, 307, 289, 274, 219. Anal. Calcd. for $C_{15}H_{10}Cl_2I_3NO_5$: C, 24.46; H, 1.36; Cl, 9.69, I, 51.77, N, 1.90; O, 10.87. Found: C, 24.68; H, 1.50; Cl, 9.57; I, 51.41; N, 2.01.

Dimethyl 5-(3-hydroxy-2-oxo-1-piperidinyl)-2,4,6-triiodo-1,3-benzenedicarboxylate (13a). Starting from **12a** (0.2 g, 0.3 mmole), methanol (15 mL) and sodium methoxide (6.3 mg, 0.3 mmole) and employing procedure D for 17 h, **13a** (0.14 g, yield 76%) was obtained as a white microcrystalline solid, after crystallization from ethyl acetate. mp: 243-245°C. tlc: R_f 0.16 in ethyl acetate -hexane (1:1). hplc: t_R 4.27 min in acetonitrile-water (7:3) at 0.5 mL / min. uv (acetonitrile): λ_{max} 241 nm, (ε 32,000). ir: 1736, 1656, 1230 cm^{-1}. ^{1}H-nmr (dimethylsulfoxide-d_6): δ 1.84-2.17 (m, 4H), 3.42 (m, 2H), 3.90 (s, 6H), 4.02 (m, 1H), 5.55 (d, 1H, J= 3.52 Hz). ^{13}C-nmr (dimethylsulfoxide-d_6) δ 19.8, 28.8, 48.2, 53.3, 67.7, 89.3, 98.6, 98.8, 147.4, 148.0, 167.9, 170.2. ms: m/z 686 (MH^+), 558. Anal. Calcd. for $C_{15}H_{14}I_3NO_6$•0.36 H_2O :C, 26.05; H, 2.15; I, 55.06; N, 2.03; O, 14.72%. Found: C, 26.21; H, 1.88; I, 54.75; N, 1.77; H_2O (KF), 0.94 % (0.36 mole).

N,N'-bis[2,3-bis(Acetyloxy)-1-propyl]-5-(3-hydroxy-2-oxo-1-piperidinyl)-2,4,6-triiodo-1,3-benzenedicarboxamide (13b). A solution of dimethylboron bromide in methylene chloride (0.5 mL; 2M) was added to **14b** (0.25 g, 0.26 mmole) in methylene chloride (5 mL) and triethylamine (0.01 mL) at 0-5°C, the mixture stirred for 8 h, and then added to saturated aqueous sodium bicarbonate (5 mL). After stirring for 5 min, ethyl acetate (50 mL) and water (10 mL) were added, the organic layer separated, washed with water, and dried. Solvent removal afforded **16b** (0.21 g), which was treated with potassium carbonate (0.25 g) in

N,N-dimethylacetamide (5 mL) following procedure B for 15 h. The mixture was filtered and concentration *in vacuo* gave a solid (0.23 g), which by HPLC was a 7:2 mixture of **13b** and the starting material **14b**. Purification by preparative TLC (hexane-ethyl acetate 1:4) furnished **13b** (0.13 g, yield 54%) as a white fluffy solid. hplc: t_R 4.5 min in acetonitrile-water (2:3) at 1 mL/min. uv (acetonitrile): λ_{max} 241 nm, (ε 29,650). ir: 3439, 1738, 1663, 1545, 1433, 1371, 1238 cm^{-1}. ^{1}H-nmr: δ 1.8-2.3 (m, 4H), 2.08 (s, 12H), 3.3-3.9 (m, 6H), 4.1-4.5 (m, 4H), 5.0 (m, 1H), 5.2 (m, 2H), 7.5 and 7.75 (2m, 2H, NH). ^{13}C-nmr: δ 20.0, 20.8, 21.2, 27.8, 39.7, 49.0, 63.2, 68.5, 70.0, 70.2, 89.5, 96.5, 147.0 (C-5 aromatic), 150.9, 169.3, 170.4, 170.5, 170.7. ms (FAB): m/z 972 $(M+H)^+$, 930, 912, 870, 844, 828, 797, 718, 671, 658, 642, 515. Anal. : Calcd. for $C_{27}H_{32}I_3N_3O_{12}$•0.78 H_2O : C, 32.92; H, 3.43; I, 38.64; N, 4.26; O, 20.75. Found: C, 33.24; H, 3.13; I, 38.34; N, 3.94; H_2O (KF) 1.42 % (0.78 mole).

N,N'-bis(2,3-Dihydroxy-1-propyl)-5-(3-hydroxy-2-oxo-1-piperidinyl)-2,4,6-triiodo-1,3-benzenedicarboxamide (13d). Method I: from 12b: Starting from **12b** (45 g, 44 mmole) methanol (220 mL), and sodium methoxide in methanol (20 mL; 0.11 M) and employing procedure D for 3 h, **13d** (29.4 g, yield 82%) was obtained as a white solid after chromatography. tlc: *Rf* 0.32 in chloroform - methanol (7:3). hplc: t_R 9.5 min by aminopropyl silica column in acetonitrile-water (8:2) at 1 mL/min. uv (acetonitrile): λ_{max} 243 nm (ε 30,200). ir: 1648, 1553, 1268 cm^{-1}. ^{1}H-nmr (dimethylsulfoxide-d_6): δ 1.8 -2.13 (m, 4H); 3.19 - 3.47 (m, 10H), 3.69 (br s, 2H), 3.99 (q, 1H); 4.47 (br s, 2H); 4.67 (br s, 2H); 5.42 (br s, 1H); 8.43 and 8.53 ppm (2 m, 2H). ^{13}C-nmr (dimethylsulfoxide-d_6): δ 19.8, 28.8, 42.6, 42.7, 48.3, 64.00, 67.8, 69.9, 91.0, 96.9, 98.16, 146.6, 150.6, 169.4, 169.8, 169.9. ms: m/z 804 $(MH)^+$, 713, 678, 587, 558, 550, 431. Anal. Calcd. for $C_{19}H_{24}I_3N_3O_8$•0.15 H_2O: C, 28.32; H, 3.04; I, 47.24; N, 5.21; O, 16.19. Found: C, 28.29; H, 3.13; I, 47.39; N, 4.97; H_2O (KF) 0.35% (0.15 mole).

Method II: from 13b: Starting from **13b** (0.03 g, 0.03 mmole), methanol (3 mL), sodium methoxide in methanol (14 mL; 0.01 M) and employing procedure D for 3 h,, **13d** (0.02 g, yield 81%) was obtained as a white solid. The HPLC t_R and the ^{1}H-NMR spectrum were identical with the sample obtained by **Method I**.

N,N'-bis[2-Hydroxy-1-(hydroxymethyl)ethyl]-5-(3-hydroxy-2-oxo-1-piperidinyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (13e). Starting from **12c** (2.0 g, 1.97 mmole), methanol (10 mL), and sodium methoxide (0.05 g, 1 mmole) and employing procedure D for 3 h, **13e** (1.1 g, yield 70%) was obtained as a colorless glass, after chromatography. mp: 260-63 °C (dec). tlc: *Rf* 0.3 in chloroform-methanol (9:1). hplc: t_R 8.8 min by aminopropyl silica column in acetonitrile-water (8:2) at 1 mL/min. uv (acetonitrile): λ_{max} 243 nm (ε 30,500). ir: 1645, 1555, 1483, 1351, 1046 cm^{-1}. ^{1}H-nmr (dimethylsulfoxide-d_6): δ 1.81-2.1 (m, 4 H),

3.52 (m, 6H), 3.63 (br d, 4H), 3.82 (m, 2H), 3.98 (m, 1H), 4.49 (br m, 4 H), 5.42 (br s, 1H), 7.68-7.55 and 8.18-8.29 (2 pairs of d, ratio 1:9, J = 6.83 Hz, 2H). ^{13}C-nmr (dimethylsulfoxide-d_6): δ 19.8, 28.7, 48.3, 52.9, 53.2, 59.3, 67.8, 90.9, 96.9, 97.7, 146.6, 150.5, 168.8, 169.9. ms: 804 (MH^+), 786, 730, 713, 678, 616, 587, 558. Anal. Calcd. for $C_{19}H_{24}I_3N_3O_8 \bullet 1.06\ H_2O$: C, 27.75; H, 3.20; I, 46.30; N, 5.11; O, 17.64. Found: C, 27.86; H, 3.00; I, 46.58; N, 4.91. H_2O (KF) 2.32% (1.06 mole).

N,N'-Bis[2,3-bis(acetyloxy)propyl]-2,4,6-triiodo-5-[{(tetrahydro-2-furanyl)carbonyl}amino]-1,3-benzenedicarboxamide (14b). Method I: from 10b: Starting from **10b** (8.73 g, 10 mmole), N,N-dimethylacetamide (30 mL), and **5** (1.8 g, 13 mmole) and employing procedure A-2 for 20 h, **14b** (6.19 g, 86% yield) was obtained as a white foam, after chromatography using hexane-ethyl acetate. mp: 101-104°C. hplc: t_R 6.04 min in acetonitrile-water (2:3) at 1 mL/min. uv (acetonitrile): λ_{max} 241 nm (ε 30,500). ir: 1740, 1667, 1545, 1479, 1371, 1233 cm^{-1}. ^{1}H-nmr: δ 1.98-2.14 (m, 2H), 2.06 (s, 12H), 2.2-2.4 (m, 2H), 3.4-4.0 (m, 6H), 4.15-4.55 (m, 4H), 5.19 (bs, 2H). ^{13}C-nmr: δ 20.7, 21.2, 25.7, 29.9, 39.7, 60.3, 69.83, 70.0, 78.5, 88.5, 98.0, 142.3, 149.6, 169.8, 170.5, 170.7. ms (FAB): m/z 972 $(M+H)^+$, 930, 912, 870, 797, 669. Anal. Calcd. for $C_{27}H_{32}I_3N_3O_{12}$: C, 33.39; H, 3.32; I, 39.20; N, 4.33; O, 19.77. Found: C, 33.39; H, 3.27; I, 38.78; N, 4.26.

Method II: from 16b: A solution of **16b** [3 mg, purity 93% by reversed phase HPLC (t_R 5.7 min, C-8 column, acetonitrile-water (1:1), 0.5 mL/min)] in acetonitrile-water (1:1) (2 mL) was stirred at room temperature for 60 h. HPLC analysis revealed that only 9% of **16b** remained, along with 3% of **13b** (t_R 4.1 min) and 70% of **14b** (t_R 4.8 min). In sharp contrast **13b** and **14b** were formed in 7:2 ratio in the presence of potassium carbonate in N,N-dimethylacetamide (see experimental for compound **13b**).

N,N'-bis(2,3-Dihydroxy-1-propyl)-2,4,6-triiodo-5-[{(tetrahydro-2-furanyl)carbonyl}amino]-1,3-benzenedicarboxamide (14d). Starting from **14b** (4.85 g, 5 mmole), methanol (50 mL), and sodium methoxide in methanol (2 mL; 0.4 M) and employing procedure D for 4 h, **14d** (3.51 g, 87% yield) was obtained as a white solid, after chromatography. mp: 202-204°C. tlc: R_f 0.5 in chloroform-methanol (9:1). hplc: Method A: t_R 7.2 min by aminopropyl silica in acetonitrile-water (4:1) at 1 mL/min. Method B: t_R: 12.5 min by aminopropyl silica in acetonitrile-water (43:7) at 1 mL/min. uv (water): λ_{max} 242 nm; (e 30,950). ir: 3360, 3304, 1653, 1551, 1495, 1352, 1269, 1069 cm^{-1}. ^{1}H-nmr (dimethylsulfoxide-d_6): 1.76-1.98 (m, 2H), 2.0-2.16 (m, 2H), 3.07-3.25 (m, 4H), 3.25-3.63 (m, 6H), 3.96-4.05 (m, 2H), 4.32 (m, 1H), 4.45 and 4.65 (br, m 4H), 8.01 (bs, 1H,), 8.38, 8.42 and 8.44 (m, 2H). ^{13}C-nmr (dimethylsulfoxide -d_6): 25.1, 29.7, 42.7, 64.0, 69.0, 70.0, 78.0, 90.0, 99.0, 99.1, 143.2, 149.9, 169.5, 169.7, 171.2. ms (FAB): m/z 804 (MH^+), 713 (M-

$NH_2CH_2CH(OH)CH_2OH$), 678 (MH-I), 585 (713-HI). Anal. Calcd. for $C_{19}H_{24}I_3N_3O_8$.•0.61 H_2O: C, 28.03; H, 3.12; I, 46.76; N, 5.16; O, 16.93. Found : C, 28.11; H, 2.99; I, 46.46; N, 5.10; H_20 (KF) 1.36% (0.61 mole).

N[3,5-bis(chlorocarbonyl)-2,4,6-triiodophenyl]tetrahydrofuran-2-carboxamide (14f). To a solution of **10f** (230.3 g, 0.39 mole) in tetrahydrofuran (276 mL) was added **5** (104 g, 0.78 mole) under nitrogen with stirring at 20 to 25°C. The solution was heated at reflux for 6 h. Heptane (552 mL) was added and the mixture again heated at reflux for 30 min. The suspension was cooled to 0 to 10°C for 2 h and filtered. The residue was crystallized from tetrahydrofuran-heptane to obtain **14f** as a crystalline solid (216.6 g, yield 81%). hplc: t_R 4.1 min by C-18 Waters Nova-Pak column 3.9 x 150 mm, 5 μ, in acetonitrile-0.2% H3PO4 (55:45) at 1 mL/min, detection at 243 nm. ir: 3329, 1788, 1767, 1686, 1491, 1476, 999 cm^{-1}. ^{1}H-nmr (300 MHz, dimethylsulfoxide-d_6): δ 1.88-2.1 (m, 2 H), 2.12-2.32 (m, 2H), 3.83-3.91 (m, 1H), 4.41-4.49 (m, 1H), 10.05 (m, 1H). ^{13}C-nmr (300 MHz, dimethylsulfoxide-d_6): δ 24.82, 29.51, 66.80, 68.85, 77.65, 99.83, 143.71, 144.55, 149.43, 168.80, 169.03, 171.39, 171.54,. ms (neg. FAB): 692 $(M-H)^-$,591, 569, 447. Anal. Calcd. for $C_{13}H_8Cl_2I_3NO_4$: C, 22.48; H, 1.15; N, 2.02; O, 9.22, total halogen, 65.12. Found: C, 22.67; H, 1.06; N, 1.90, total halogen, 64.89.

2-(Acetyloxy)-N-[3,5-bis(chlorocarbonyl)-2,4,6-triiodophenyl]-5-bromopentanamide (15f). To a stirred solution of **14f** (100 g, 0.144 mole) in dry methylene chloride (1 L) was added boron tribromide (18.03 g, 0.072 mole) at room temperature. The mixture was stirred for 1 h and acetic anhydride (29.21 g, 0.288 mole) was added to the solution of the bromoboronate intermediate and the mixture heated to reflux for 4 h. Methylene chloride (0.5 L) was distilled out and replaced by heptane (0.5 L) maintaining the temperature at 35-40°C. The resulting slurry was kept at 0-5°C for 1 h and filtered. The residue was washed with cold methylene chloride-heptane (1:1) (0.3 L) and dried to obtain **15f** as a white crystalline solid (98.5 g, yield 85%). hplc: t_R 21.6 min by Chromegabond MC-18-3 column 4.6 x 100 mm, 3 μ, in acetonitrile-0.03 M dibasic potassium phosphate (50:50), pH 3.0, at 1 mL/min, detection at 245 nm. ir: 3391, 1765, 1695, 1481, 1358, 1225, 991 cm^{-1}. ^{1}H-nmr (300 MHz, dimethylsulfoxide-d_6): δ 1.95-2.20 (m, 4H), 2.15 (s, 3H), 3.58 (t, 2H, J=7Hz), 5.22 (m, 1H), 10.22-10.35 (m, 1H). ^{13}C-nmr (300 MHz, dimethylsulfoxide-d_6): δ 20.25, 27.75, 29.36, 33.80, 71.65, 85.30, 99.25, 142.85, 143.35, 149.39, 167.40, 168.70, 169.12. ms (FAB): 816 and 818 $(M+H)^+$ (halogen isotopes), 782, 780, 736, 700, 654, 595, 567, 550. Anal. Calcd. for $C_{15}H_{11}BrCl_2I_3NO_5$: C, 22.04; H, 1.35; N, 1.71; total halogen, 65.11; O, 9.79. Found: C, 22.17; H, 1.53; N, 2.04; total halogen, 65.71.

(5S-trans)-3-[3-(Acetyloxy)-2-oxo-1-piperidinyl]-5-[[(6-hydroxy-2,2-dimethyl-1,3-dioxepan-5-yl)amino]-carbonyl]-2,4,6-triiodobenzoyl chloride (18). A solution of **12f** (6.6 g, 9 mmole) in dry N,N-

dimethylacetamide (40 mL) and triethylamine (0.90 g, 9 mmole) was treated with **17**[16] (1.6 g, 9.9 mmole) at ambient temperature for 16 h. Evaporation of volatiles, partitioning between ethyl acetate (150 mL) and water (100 mL), drying, followed by chromatography (ethyl acetate:hexane) afforded **18** (5.3 g, yield 84%) as a colorless glass. ir: 1970, 1742, 1221, 1047 cm^{-1}. ^{1}H-nmr: δ 1.36 (s, 6H), 2.16 (s, 3H), 2.32 (m, 2H), 3.2 - 4.1 (overlapping m, 12H), 5.41 (br s, 1H), 8.8 (br s, 1H). ^{13}C-nmr: δ 20.7, 25.0, 26.9, 48.8, 54.7, 62.0, 69.4, 69.6, 86.5, 93.5, 94.0, 98.5, 102.5, 147.8, 150.1, 150.2, 166.5, 170.3. ms: m/z 860.8 (MH^+), 802.8. Anal. Calcd. for $C_{22}H_{24}ClI_3N_2O_8$: C, 30.70; H, 2.81; Cl, 4.12; I, 44.24; N, 3.26; O, 14.87. Found: C, 30.89; H, 2.73; Cl, 4.08; I, 43.86; N, 3.42.

N-[[1,3,4-Trihydroxy-2-butyl]-5-[3-hydroxy-2-oxo-1-piperidinyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (21). A mixture of **18** (4.4 g, 5.1 mmole), dry N,N-dimethylacetamide (20 mL), and liquid ammonia (4 mL) was stirred at room temperature for 18 h in a steel bomb. Excess ammonia was allowed to evaporate. The resulting residue **19** was treated with 5 M sodium hydroxide (2.0 mL) for 2 h. The pH of the mixture containing **20** was then adjusted to 0.5 with concentrated hydrochloric acid and the mixture stirred for 16 h. The volatiles were removed and the residue was chromatographed as per procedure D to obtain **21** as a glassy solid (3.42 g, yield 88%). ir: 3450, 1659, 1528, 1350 cm^{-1}. ^{1}H-nmr (dimethylsulfoxide-d_6 /deuterium oxide): δ 1.75 - 2.25 (overlapping m, 4H), 3.30 (br s, 1H), 3.53 and 3.64 (2 overlapping br s, 5H), 3.92 (m, 2H). ^{13}C-nmr (dimethylsulfoxide-d_6 /deuterium oxide): δ 19.7, 19.9, 28.5, 48.2, 51.5, 52.0, 58.5, 63.2, 67.6, 69.0, 90.5, 91.0, 93.5, 98.5, 146.5, 150.3, 166.5, 169.8, 170.3. ms: m/z (NH_3 DEP) 777 ($M+NH_4^+$), 760 (MH^+). Anal. Calcd. for $C_{17}H_{20}I_3N_2O_7$: C, 26.90; H, 2.66; I, 50.15; N, 5.54; O, 14.75. Found: C, 26.96; H, 2.81; I, 50.54; N, 5.38.

2,4-Dibromobutyryl bromide (26p)[17b]. To a mixture of **25p** (49.2 g, 0.57 mole) and red phosphorus (6.54 g, 0.21 mole) , cooled to 0°C under nitrogen, was added dropwise bromine (95.9 g, 0.60 mole) over 1 h, maintaining the internal temperature < 10°C. The reaction mixture was then brought to 70°C and an additional 95.9 g portion of bromine was added over 1 h. The reaction mixture was heated at 80°C for 3.5 h and then distilled *in vacuo*. Residual bromine and hydrogen bromide were first removed and the residue distilled *in vacuo* to obtain **26p**, (120.7 g, yield 68%), as a clear, slightly pink oil. bp: 61- 65°C (0.25-0.35 mm Hg); density: 2.245 g/mL; ir (chloroform): 1784 , 1435, 1258, 999 cm^{-1} ; ^{1}H-nmr: δ 2.40-2.80 (m, 2H); 3.40-3.70 (m, 2H); 4.70-5.00 (m, 1H). ^{13}C-nmr: δ 28.53, 36.78, 56.81, 165.10. ms: m/z (NH_3/DEP) 263$^+$ ($M+NH_4$). Anal. Calcd. for $C_5H_7Br_3O$: C, 15.56; H, 1.63; Br, 77.63; O, 5.18. Found: C, 15.53; H, 1.60; Br, 77.36 .

2,5-Dibromopentanoyl bromide (26q). The compound was prepared from **25q** (75 g, 0.75 mole) and red phosphorus (8.7 g, 0.28 mole) by the procedure employed for **26p**. The crude product was purified by distillation twice under reduced pressure to give **26q** as a slightly colored liquid (220 g, yield 90%). bp: 64-66°C, (0.1 mm Hg); gc: (as methyl 2,5-dibromovalerate) OV 101 (6 x 1/8") column; Injection port temperature, 240°C, column temperature 120-220°C (temperature program rate 20°C/min); flow rate, 60 mL/min), t_R 3.72 min, purity 96%. ^{1}H-nmr: δ 2.2 (m, 2H); 2.30-2.45 (2m, 2H); 3.54 (t, 2H, J=6.5 Hz); 4.71 (dd, 1H, J_1, =7.9 Hz, J_2=5.6 Hz). ^{13}C-nmr: δ 29.0, 31.6, 33.1, 57.4, 165.3. ms: m/z 245, 243, 241(2 bromine isotope cluster , M-Br$^+$), 217, 215, 213, 165, 163, 135, 133. Anal: Calcd. for $C_5H_7Br_3O$: C, 18.60; H, 2.19; Br, 74.26; O, 4.9. Found: C, 18.51; H, 2.14; Br, 73.84.

2,6-Dibromohexanoyl bromide (26r). The compound was prepared from **25r** (6.0 g, 52.5 mmole), red phosphorus (0.6 g, 19.9 mmole) and bromine (18.4 g, 115 mmole, added in two portions) by the procedure employed for **26p**. Distillation of the crude residue provided **26r** as a clear colorless liquid (5.20 g, 78% yield). bp: 90-92°C (0.15 mm Hg). ^{1}H-nmr: δ 1.71 (m, 2H), 1.93 (m, 2H), 2.17 (m, 2H), 3.43 (t, 2H, J=6.6 Hz), 4.58 (dd, 1H, ABX system, J_{ax} = 7.26 Hz, J_{bx} = 5.94 Hz). ^{13}C-nmr: δ 25.5, 31.6, 32.6, 33.8, 57.9, 165.6. Anal. Calcd. for $C_6H_9Br_3O$: C,21.39; H, 2.69; Br, 71.76. Found: C, 21.76; H, 2.69; Br, 71.43.

N,N'-bis-[2,3-bis-(acetyloxy)-1-propyl]-5-[3-chloro-2,2-dimethyl-1-oxo-propyl]-amino-2,4,6-triiodo-1, 3-benzenedicarboxamide (28b). Starting from **10b**[1c] (10.0 g, 11.4 mmole), N,N-dimethylacetamide (25 mL) and **22** (10.6 g, 68.4 mmole) and employing procedure A-1 for 70 h at 60°C, **28b** (7.22 g, yield 64%) was obtained as a light yellow solid, after chromatography using a step gradient of methanol in chloroform (0-5%). mp: 119.5 - 132.0°C (dec). tlc: *Rf* 0.32 in methanol-chloroform (1:19). hplc: t_R 4.61 min in acetonitrile-water (6:4) at 0.5 mL/min. uv: (methanol) λ_{max} 241 nm (ε = 56,200). ir: 3400, 1740, 1665 cm^{-1}. ^{1}H-nmr: δ : 5.20 (m, 2H), 4.40-4.21 (m, 4H), 3.77 (s, 2H), 3.75-3.58 (m, 4H), 2.12 (s, 12H), 1.52 (bs, 6H). ^{13}C-nmr: δ 21.3, 21.5, 23.3, 39.9, 44.8, 52.6, 63.6, 70.0, 88.0, 98.8, 143.47, 149.9, 170.3, 170.5, 170.8, 170.9, 173.9. ms: m/z 992 (MH$^+$), 932, 864. Anal. Calcd. for $C_{27}H_{33}N_3ClI_3O_{11}$•0.78 H_2O: C, 32.24; H, 3.46; N, 4.18; Cl, 3.52; I 37.85; O, 18.74. Found: C, 32.61; H, 3.09; N, 3.81; Cl, 3.55; I, 38.15; H_2O (KF) 1.4% (0.78 mole).

N,N'-bis-[2,3-bis-(Acetyloxy)-1-propyl]-5-[4-chloro-1-oxo-butyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (29b). Starting from **10b**, (87.3 grams, 100 mmole), N,N-dimethylacetamide (370 mL) and **23** (20.87 g, 0.15 mole) and employing procedure A-1 for 68 h, **29b** (82.45 g, yield 84%) was obtained as an off white powder, after precipitation from ethyl acetate with hexanes. mp: 211.1-213.6°C. tlc:

Rf 0.28 in ethyl acetate-methylene chloride (4:1). hplc: t_R 14.18 min. in acetonitrile-water (3:7) isocratic 2 min, then ramp to acetonitrile-water(3:2) over 15 min then hold for 8 min at 1.0 mL/min. uv (acetonitrile): λ_{max} 241.2 nm (ε_{max} 28,000). ir: 3253, 3080, 3060, 1741, 1656, 1548, 1231 cm^{-1}. ^{1}H-nmr (dimethylsulfoxide-d_6) δ 2.04 (s, 12H), 2.11 (m, 2H), 2.49 (t, 2H, J=7Hz), 3.48 (m, 4H), 3.76 (t, 2H J=6.5Hz), 4.25 (m, 4H), 5.11 (t, 2H, J=5Hz), 8.55, 8.65, 8.79 and 8.91(4m, 2H), 10.07 (s, 1H) ppm. ^{13}C-nmr: (dimethylsulfoxide-d_6) δ 20.6, 21.0, 27.9, 32.6, 38.8, 45.0, 63.0, 69.5, 89.9, 99.1, 99.2, 99.3, 99.4, 143.2, 149.8, 169.6, 169.7, 169.9, 170.2. ms: m/z 977.8 (MH^+), 935.9, 917.9, 852.1. Anal. Calcd. for $C_{26}H_{31}N_3ClI_3O_{11}\bullet 0.3H_2O$: C, 31.77; H, 3.24 N, 4.27; Cl, 3.61; I, 38.73; O, 18.0%. Found : C, 31.17; H, 3.09; N, 3.99; Cl, 3.14; I, 38.44. H_2O (KF) 0.54 % (0.3 mole).

Dimethyl 5-[(2,5-dibromo-1-oxopentyl)amino]-2,4,6-triiodo-1,3-benzenedicarboxylate (31a). Starting from **10a** (1.79 g, 3 mmole), N,N-dimethylacetamide (13 mL) and **26q** (1.94 g, 6 mmole) and employing procedure A-2 for 20 h, **31a** (1.66 g, yield 67%) was obtained as a white crystalline solid, after crystallization from hexane-ethyl acetate (15 mL, 1:2.5). mp 260°C (dec). tlc: *Rf 0.5* ethyl acetate-hexane (1:3). hplc: t_R 8.16 min in acetonitrile-water (7:3) at 0.5 mL/min. uv (acetonitrile) λ_{max} 242.8, (ε 31,039). ir: 1733; 1676.9, 1522, 1233.2 cm^{-1}. ^{1}H-nmr (dimethylsulfoxide-d_6) δ 1.99-2.09 (m, 2H); 2.09-2.25 (m, 2H); 3.60 (t, J = 6.4 Hz, 2H); 3.91 (s, 6H); 4.65 (t, J = 7.03 Hz, 1H); 10.5 (s, 1 H). ^{13}C-nmr (dimethylsulfoxide -d_6) δ 30.1 , 33.1, 33.9, 47.3, 53.3, 88.9, 99.3, 99.7, 142.6, 147.6 147.8 166.2, 167.9. ms: m/z 827,829,831(2 Br isotope cluster) (MH^+); 795,797,799 (2 Br isotope cluster, M-OCH_3^+); 747,749 (Br isotope cluster, M-Br). Anal. Calcd. for $C_{15}H_{14}O_5Br_2I_3N\bullet 0.51\ H_2O\bullet 0.21\ CH_3COOC_2H_5$. C, 22.21; H, 1.97; Br, 18.66; I, 44.45; N, 1.64; O, 11.08. Found: C, 21.98; H, 1.56; Br, 18.67; I, 44.48; N, 1.57. H_2O (KF) 1.10% (0.51 mole); $CH_3COOC_2H_5$ (TGFTIR) 2.16% (0.2 mole).

N,N'-bis[2,3-bis-(Acetyloxy)-1-propyl]-5-[(2,5-dibromo-1-oxopentyl)amino]-2,4,6-triiodo-1,3-benzenedicarboxamide (31b). Starting from **10b** (23.0 g, 26.3 mmole), N,N-dimethylacetamide (240 mL) and **26q** (11.1 g, 34.2 mmole) and employing procedure A-2 for 21 h, **31b** (20.2 g, yield 69%) was obtained as an off-white amorphous solid. mp: 135-140 °C (dec). tlc: *Rf* 0.39 ethyl acetate-hexane (8:2). hplc: Method A: t_R 3.87 min in 70% acetonitrile-water at 0.5 mL/min; Method B: t_R 15.7 min in 40% acetonitrile-water at 1 mL/min. uv (acetonitrile): λ_{max} 242 nm, (ε 29,100). ir: 1738, 1653, 1546, 1238 cm^{-1}. ^{1}H-nmr (dimethylsulfoxide-d_6) δ 2.03-2.14 (m, 4H), 2.09 (s, 12H), 3.47-3.61 (m, 4H) 3.67 (t, 2H, triplet, J = 6.5 Hz); 4.22-4.38 (2 dd, 4H, ABX pattern, δ_{AB}= 32.5 Hz, J_{AB}= 11.86 Hz, J_{AX} = 5.56 Hz); 4.70 (t, 1H, J = 7.03 Hz), 5.16 (m, 2H); 8.58, 8.71, 8.81, 8.95 (4t, 2H, J = 5.57 Hz); 10.48 (s, 1H). ^{13}C-nmr (dimethylsulfoxide -d_6) δ 20.5, 21.0, 30.1, 33.1, 34.0, 38.9, 47.45, 47.53, 63.0, 69.5, 90.4, 98.3, 98.6, 141.9, 149.9, 150.08, 165.83, 165.89,

169.5, 169.8, 170.1. ms: m/z 1118, 1116, 1114 (2 bromine isotope cluster, MH^+), 1074, 1058, 1056, 1054, 1014, 813, 735,733, 699, 625. Anal. Calcd. for $C_{27}H_{32}Br_2I_3N_3O_{11}$: C, 29.08; H, 2.89; N, 3.77; Br, 14.33; I, 34.14; O, 17.96. Found: C, 29.14; H, 3.02; N, 3.65; Br, 14.32; I, 34.13.

N,N'-bis[2-(Acetyloxy)-1-[(acetyloxy)methyl]ethyl]-5-[(2,5-dibromo-1-oxopentyl)amino]-2,4,6-triiodo-1,3-benzenedicarboxamide (31c). Starting from **10c** (15.9 g, 49.3 mmole), N,N-dimethylacetamide (250 mL) and **26q** (20.8 g, 64.1 mmole) and employing procedure A-2 for 22 h, **31b** (35.3 g, yield 84%) was obtained as an off-white crystalline solid after crystallization from ethyl acetate. mp: 240-243 °C. tlc: *Rf* 0.46 ethyl acetate - hexane (8:2). hplc: t_R, 3.8 min in acetonitrile-water (7:3) at 0.5 mL/min. uv: (acetonitrile): λ_{max} 242 nm (ε 32,100). ir: 1733, 1668, 1650, 1545, 1242 cm^{-1}. ^{1}H-nmr (dimethylsulfoxide -d_6) δ 1.98-2.08 (m, 2H); 2.04 (s, 12H), 2.1-2.15 (m, 2H); 3.61 (t, 2H, J=6.16 Hz); 4.14-4.19 (d, 8H), 4.33-4.35 (m, 1H); 4.64 (t, 1H, J=6.74 Hz); 8.82 and 8.95 (d, 2H , J=7.70 Hz); 10.42 (d, 1H). ^{13}C-nmr (dimethylsulfoxide -d_6) δ 20.7, 30.2, 33.1, 34.0, 47.0, 47.4, 62.0, 90.4, 98.5, 98.8, 142.0, 149.7, 149.8, 165.8, 168.9, and 170.2. ms: m/z 1116, 1114, 1112 (2 bromine isotope cluster, MH^+), 1076, 1074, 1072, 1058, 1056, 1054, 992, 990, 988. Anal. Calcd. for $C_{27}H_{32}Br_2I_3N_3O_{11}$: C, 29.08; H, 2.89; Br, 14.33;I, 34.14; N, 3.78; O, 15.78. Found: C, 29.04; H, 2.77; Br, 14.24; I, 33.92; N, 3.78.

N,N'-bis[2,3-bis(Acetyloxy)-1-propyl]-5-[(5-chloro-1-oxopentyl)amino]-2,4,6-triiodo-1,3-benzene-dicarboxamide (32b). Starting from **10b** (20.5 g, 23 mmole), N,N-dimethylacetamide (75 mL) and **24** (5.1 g, 33 mmole) and employing procedure A-1 for 30 h, **32b** (22.1 g, yield 97%) was obtained as an off-white foamy solid. hplc: t_R 8.0 min in acetonitrile-water (45:55) at 0.5 mL/min. ir: 1740, 1655, 1545, 1372, 1232.6 cm^{-1}. ^{1}H-nmr: δ 2.01 (bs, 2H), 2.11 (s, 6H), 2.14 (s, 6H), 2.59 (bs, 2H), 3.55 (t, 2H, J=5.9 Hz), 3.63 (bp, 2H), 4.24 (m, 2H), 4.44 (m, 2H), 5.28 (m, 2H), 7.95, 8.4, 9.55, 9.85 (NH). ^{13}C-nmr: δ 20.8, 21.4, 21.5, 32.1, 35.5, 44.7, 66.7, 70.0, 87.0, 98.0, 143.0, 149.0, 149.5, 170.3, 170.4, 170.6, 170.7, 171.6. ms: m/z 992 (MH^+), 950, 932, 890, 866, 817, 689, 647, 563. Anal. Calcd. for $C_{27}H_{33}ClIN_3O_{11}$: C, 32.70; H, 3.35; Cl, 3.57; I, 38.39; N, 4.24. Found: C, 32.63; H, 3.40; Cl, 3.61; I, 38.81; N, 4.13.

N,N'-bis[2,3-bis(Acetyloxy)-1-propyl]-5-[(2,6-dibromo-1-oxohexyl)amino]-2,4,6-triiodo-1,3-benzene-dicarboxamide (33b). Starting from **10b** (3.98 g, 4.7 mmole), N,N-dimethylacetamide (10 mL) and **26r** (2.07 g, 6.1 mmole) and employing procedure A-2 for 21 h, **33b** (5.1 g, yield 95%) was obtained as a pale yellow solid. tlc: *Rf* 0.30 ethyl acetate-hexane (5:1). hplc: t_R 12.4 min in acetonitrile-water (1:1) at 0.5 mL/min. ir: 1742, 1655, 1545, 1231 cm^{-1} . ^{1}H-nmr (dimethylsulfoxide -d_6) δ 1.64 (m, 2H), 1.85 (m, 2H), 2.12 (m, 14H), 3.45 (m, 6H), 4.27 (m, 4H), 4.61 (t, 1H), 5.12 (br s, 2H), 8.80 (br t, 1H), 8.93 (br t, 1H) and

10.42 (s, 1H). ^{13}C-nmr (dimethylsulfoxide -d_6) δ 20.9, 21.4, 25.7, 31.8, 35.1, 38.8, 48.8, 63.3, 69.8, 91.0, 99.0, 142.3, 150.4, 166.4, 169.9, 170.2, 170.5. ms: m/z 1127 (MH+), 1069. Anal. Calcd. for $C_{28}H_{34}N_3O_{11}I_3Br_2$: C, 29.79; H, 3.04; N, 3.72; Br, 14.15; I, 33.72; O, 15.59. Found: C, 29.81, H, 3.01; N, 3.40; Br, 14.03; I, 33.42.

N, N'-bis-[2, 3-bis-(Acetyloxy)-1-propyl]-5-[3, 3-dimethyl-2-oxo-1-azetidinyl]-2, 4, 6-triiodo-1,3-benzenedicarboxamide (34b). Starting from **28b** (7.0 g, 7.1 mmole), N,N-dimethylacetamide (40 mL), and potassium carbonate (7.0 g, 50 mmole) and following procedure B for 20 h, a mixture resulted from which the solvent was removed *in vacuo*, the residue dissolved in ethyl acetate (300 mL) and the solution washed with water (3 x 100 mL). Drying of the organic layer, solvent removal, and crystallization from ethyl acetate/ hexane (5 : 1) afforded analytically pure **34b** (5.6 g, Yield 83%) as a white solid. mp: 212.0- 213.0°C. tlc: *Rf* 0.40 in chloroform-methanol (19:1). hplc: t_R 4.51 min in acetonitrile-water (3:2) at 0.5 mL/min. uv (methanol): λ_{max} 244.4 nm (ε 52,600). ir: 3300, 1744, 1657 cm^{-1}. ^{1}H-nmr: δ 1.49 (s, 6H), 2.10 (s, 12 H), 3.67 (s, 2H), 3.69 (m, 4H), 4.40-4.25 (m, 4H), 5.20 (m, 2H). ^{13}C-nmr: δ 20.8, 21.3, 39.9, 52.1, 55.1, 63.4, 70.2, 91.0, 97.4, 141.0, 150.4, 170.5, 170.8. ms: m/z 956 (MH^+), 896. Anal. Calcd. for $C_{27}H_{32}N_3I_3O_{11}$: C, 33.95; H, 3.38; N, 4.40; I, 39.85; O, 18.42. Found: C, 33.95; H, 3.51; N, 4.34; I, 40.00.

N,N'-bis-[2,3-Dihydroxy-1-propyl]-5-[3,3-dimethyl-2-oxo-1-azetidinyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (34d). Starting from **34b** (5.75 g, 6 mmole), methanol (20 mL), and sodium methoxide in methanol (5 mL; 1.4 M) and employing procedure D for 1 h, **34d** (4.3 g, yield 90.7 %) was obtained as a colorless glass. mp. 185 - 198°C (dec). hplc: t_R 5.48 min by aminopropyl silica in acetonitrile-water (4:1) at 1.0 mL/min. uv (methanol): λ_{max} 244 nm (ε = 55,000). ir: 3450, 1651 cm^{-1}. ^{1}H-nmr: δ 1.45 (s, 6H), 3.70-3.17 (m, 12H), 4.51 and 4.72 (m, 2H), 8.48 and 8.60 (2t, 2H). ^{13}C-nmr: δ 19.6, 42.1, 50.9, 56.0, 63.5, 69.6, 90.9, 97.1, 140.6, 149.2, 171.7, 174.9. ms: m/z 805 (M + NH_4^+), 788 (MH^+). Anal. Calcd. for $C_{19}H_{24}N_3I_3O_7$•0.92 H_2O: C, 28.40; H, 3.24; N, 5.23; I, 47.37. Found: C, 28.13; H, 3.05; N, 5.36; I, 47.06; H_2O (KF) 2.06% (0.92 mole).

Dimethyl 5-(2-oxo-1-pyrrolidinyl)-2,4,6-triiodo-1,3-benzenedicarboxylate (35a). Starting from **10a** (5.87 g, 10 mmole), N,N-dimethylacetamide (20 mL) and **23** (1.76 g, 12.5 mmole) and employing first procedure A-1 for 36 h and then procedure B with potassium carbonate (5.52 g, 40 mmole) for 72 h, a mixture resulted, which was diluted with acetonitrile (75 mL), the salts filtered off, solvents removed, and the residue partitioned between ethyl acetate-methylene chloride (4:1) (250 mL) and water. Drying of the organic layer, solvent removal, and crystallization from ethyl acetate-methanol-hexanes provided **35a** (4.70 g, yield 72%) as a crystalline solid. mp: 186.8-187.8°C. ir: 2955, 1730, 1688, 1522, 1414, 1225, 1130 cm^{-1}. ^{1}H-nmr: δ 2.30 (m,

2H), 2.55 (t, 2H), 3.72 (t, 2H), 3.96 (s, 6H). ^{13}C-nmr: δ 19.4, 31.1, 47.2, 53.5, 87.8, 96.5, 144.6, 148.8, 167.7, 173.64. ms: (NH_3 DEP) m/z 673 ($M+NH_4^+$), 656 (MH^+), 528. Anal. Calcd. for $C_{14}H_{12}I_3NO_5$: C, 25.67; H, 1.85; I, 58.13; N, 2.14; O, 12.21. Found: C, 25.73; H, 1.62; I, 58.44; N, 2.17.

For the further processing of the mother liquor from the crystallization see the procedure for compound **44a**.

N,N'-bis-[2,3-bis-(Acetyloxy)-1-propyl]-5-[2-oxo-1-pyrrolidinyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (35b). Starting from **29b** (55.36 g, 56.6 mmole), N,N-dimethylacetamide (500 mL), and potassium carbonate (54.8 g, 0.4 mole) and employing procedure B for 44 h, a mixture resulted, which was filtered, solvent removed from the filtrate *in vacuo*, and the resulting thick syrup partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate, the combined organic layers dried and the solvent removed to obtain a foam (50.23 g), 44.5 g of which was purified by chromatography using methylene chloride /ethyl acetate mixtures. Fractions 140-162 gave **35b** (25.42 g, 47% yield, contains 0.3 % compound **44b**). mp: 129.6 - 133.1°C. tlc R_f 0.13 in ethyl acetate-methylene chloride (4:1). hplc: t_R 11.1 min. in acetonitrile-water (3:7) isocratic elution 2 min, then ramp to acetonitrile-water (3:2) in 15 min, then hold 8 min at 1.0 mL/min. UV (acetonitrile): λ_{max} 242.2 nm (ε_{max} 27,540). ir: 3438, 2953, 1739, 1672, 1548, 1239 cm^{-1}. ^{1}H-nmr (dimethylsulfoxide -d_6) δ 2.11 (s, 12H), 2.31 (m, 2H), 2.49 (t, 2H, J=8 Hz), 3.56 (m, 4H), 3.70 (t, 2H), 4.32 (m, 4H), 5.17 (br s, 2H), 8.70 - 9.10 (4m, 2H). ^{13}C-nmr (dimethylsulfoxide -d_6): δ 19.0, 20.6, 21.04, 30.69, 38.79, 46.80, 63.00, 69.50, 91.59, 97.93, 98.14, 98.31, 143.91, 150.28, 150.33, 169.43, 169.47, 169.87, 170.18, 172.73. ms: m/z 941.9 (MH^+), 899.9, 881.9, 839.9, 814.0. Anal. Calcd. for $C_{26}H_{30}N_3I_3O_{11}$•0.78 H_2O : C, 32.69; H, 3.33; N, 4.40; I, 39.85; O, 19.73%. Found : C, 33.07; H, 3.27; N, 4.11; I, 40.11. H_2O (KF) 1.47 % (0.78 mole).

For the processing of chromatographic fractions 1-56 see the procedure for compound **44b**.

N,N'-bis-[2,3-Dihydroxy-1-propyl]-5-[2-oxo-1-pyrrolidinyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (35d). Starting from **35b** (24.88 g, 26.6 mmole), methanol (200 mL) and sodium methoxide in methanol (10 mL, 0.65M) and employing procedure D for 7h, **35d** (13.87 g, yield 67%) was obtained as a white amorphous powder. mp: >265 °C. tlc: R_f 0.28 in methylene chloride-methanol (4:1). hplc: t_R 7.39 min by aminopropyl silica; in acetonitrile-water (4:1) at 1.0 mL/min. uv (acetonitrile) λ_{max} 243.0 nm (ε_{max} 27,950). ir: 3390, 2934, 1653, 1558, 1270, 1044 cm^{-1}. ^{1}H-nmr (dimethylsulfoxide -d_6) δ 2.33 (q, 2H, J=6 Hz), 2.49 (t, 2H, J=8 Hz), 3.22 (m, 2H), 3.50 (4H, m, overlapped by residual H_2O in dimethylsulfoxide-d_6), 3.74 (2m, 4H), 4.59 (m, 2H) 4.80 (app. t, 1.43H, J=4.5 Hz), 4.88 (app t, 0.57H, J=4.0 Hz), 8.29 (m, 0.40H, NH), 8.57 (t, 0.79H, J=5Hz, NH), 8.68 (br t, 0.79H, NH). ^{13}C-nmr (dimethylsulfoxide -d_6) δ 19.07, 30.77, 42.58,

42.66, 46.86, 63.96, 63.99, 69.99, 70.09, 91.88, 98.18, 98.26, 143.70, 150.51, 169.40, 172.73. ms: m/z 773.8 (MH^+), 682.7, 647.9, 520.0. Anal. Calcd. for $C_{18}H_{22}N_3I_3O_7 \bullet 0.86\ H_2O$: C, 27.41; H, 3.03; N, 5.33; I, 48.27; O, 15.97. Found: C, 27.24; H, 2.97; N, 5.13; I, 48.52. H_2O (KF) 1.97% (0.86 mole).

Dimethyl 5-(3-bromo-2-oxo-1-pyrrolidinyl)-2,4,6-triiodo-1,3-benzenedicarboxylate (36a). Starting from **10a** (1.17 g, 2.0 mmole), N,N-dimethylacetamide (6.7 mL), and **26p** (1.0 g, 3.6 mmole) and employing procedure A-2 for 19.5 h, **30a** (1.83 g), containing **36a**, was obtained as tan crystals. **30a** (0.92 g, 1.1 mmole), in N,N-dimethylacetamide (11 mL) and potassium carbonate (0.2 g, 1.5 mmole) was treated according to procedure B for 35 min, resulting in a mixture from which the solvent was removed, ethyl acetate (50 mL) added, and the organic layer washed with 10% hydrochloric acid, brine, and dried. Solvent removal gave a crude foam, which was crystallized from boiling ethyl acetate/methanol /hexane to obtain **36a** (0.62 g, yield 52%) as off-white crystals. mp: 233-235°C. tlc: R_f 0.32 in hexanes-ethyl acetate (3:1). hplc: t_R 5.75 min in acetonitrile-water (7:3) at 0.5 mL/min. uv (acetonitrile): λ_{max} 243 nm (ε 34,000). ir: 1732, 1702, 1416, 1226 cm^{-1}. ^{1}H-nmr: δ 2.58 (m, 1H), 2.98 (m, 1H), 3.60 (m, 1H), 4.00 (m, 1H), 3.978 (s, 3H), 3.985 (s, 3H), 4.55 (dd, 1H). ^{13}C-nmr: δ 31.9, 43.2, 45.8, 53.9, 88.9, 96.1 and 97.0, 143.7, 149.3, 149.7, 168.1, 168.9. ms: m/z 734 (MH^+), 702, 655, 608. Anal. Calcd. for $C_{14}H_{11}NO_5BrI_3$: C, 22.91; H, 1.51; N, 1.91; O, 19.90; Br, 10.89; I, 51.88. Found: C, 23.04; H,1.35 ; N, 1.90; I, 52.02; Br, 10.92.

N,N'-bis-[2,3-bis-(Acetyloxy)-1-propyl)]-5-[3-bromo-2-oxo-1-pyrrolidinyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (36b). Starting from **10b** (91.7 g, 0.11 mole), N,N-dimethylacetamide (500 mL), and **26p** (41.8 g, 0.14 mole) and following procedure A-2 for 70 h and then procedure B with potassium carbonate [(I) 37.7 g, 0.27 mole; (II) 18.9 g, 0.14 mole] for 9 h, a mixture resulted, that was filtered, the filtrate concentrated to 150 mL *in vacuo*, poured into iced water (1.4 L) and then cooled at 5°C overnight. The resulting precipitate was filtered, dried, and then chromatographed using ethyl acetate:hexanes to obtain **36b** (60.72 g, yield 57%) as an off-white foam. tlc: R_f = 0.25 in ethyl acetate-hexanes (4:1); hplc: t_R 14.4 min by isocratic elution 2 min at 20% acetonitrile-water followed by gradient elution 20-70% acetonitrile into water over 13 min. uv (acetonitrile) λ_{max} 243 nm (ε 29,300). ir: 1724, 1671, 1540, 1419, 1373, 1245 cm^{-1} ; ^{1}H-nmr (dimethylsulfoxide-d_6) δ 2.03 (s, 12 H); 2.50 (m, 1H); 2.97 (m, 1H); 3.50 (m, 4H); 3.60 (m, 1H) 3.83 (m, 1H); 4.24 (d, 4H); 4.88 (m, 1H); 5.09 (br s, 2H); 8.67, 8.78, and 8.94 (m, 2H); ^{13}C-nmr (dimethylsulfoxide-d_6): δ 20.61, 21.04, 31.11, 38.79, 44.58, 45.32, 62.97, 69.49, 92.31, 97.28, 142.56, 150.38, 150.51, 168.06, 169.32, 169.39, 169.87 and 170.18; ms: m/z 1020/1022(MH^+), 962, 920, 894. Anal. Calcd. for $C_{26}H_{29}N_3O_{11}BrI_3$: C, 30.61; H, 2.87; N, 4.12; Br, 7.83; I, 37.32; O, 17.25. Found : C, 30.58; H, 2.82; N, 4.08; Br, 7.79; I, 37.09.

N,N'- bis - [2-Acetyloxy - 1 - [acetyloxymethyl] - ethyl - 5 - [3 - bromo - 2 - oxo - 1 - pyrrolidinyl] - 2,4,6 - triiodo - 1,3 - benzenedicarboxamide (36c). Starting from **10c** (91.7 g, 0.11 mole), N,N-dimethylacetamide (500 mL), and **26p** (41.8 g, 0.14 mole) and following procedure A-2 for 5 h and then procedure B with potassium carbonate [(I) 37.2 g, 0.27 mole; (II) 18.6 g, 0.14 mole] for 3 h, a mixture resulted, from which the salts were filtered off, solvent removed *in vacuo*, and the oily residue poured into iced water (1.5 L). The resulting precipitate was dried and then crystallized from acetonitrile to obtain **36c** (79.8 g, yield 75%) as an off-white solid. mp: 243.5-244.5 °C. tlc: Rf 0.37 in ethyl acetate-hexanes (4:1). hplc: t_R 13.98 min by isocratic elution at 1 mL/min at 20% acetonitrile-water for 2 min, then ramp to 60% acetonitrile over 15 min and hold at 60% 10 min at 1.0 mL/min. uv (acetonitrile): λ_{max} 243.4 nm, ε (29,800). ir: 3300, 1727, 1666, 1546, 1244 cm^{-1}. ^{1}H-nmr (dimethylsulfoxide-d_6) δ 2.04, 2.05 (s, 12H), 2.49 (m, 1H), 2.95 (m, 1H), 3.54 (m, 1H), 3.83 (br q, 1H), 4.14 and 4.16 (br s, 8H), 4.34 (br s, 2H), 4.87 (m, 1H), 8.60 and 8.70 (m, total 0.4H, NH), 8.81 (m, 0.8H, NH), 9.00 (app t, 0.8H, NH). ^{13}C-nmr (dimethylsulfoxide-d_6) δ 20.75, 31.10, 44.59, 45.29, 46.98, 62.04, 92.20, 97.78, 98.11, 142.61, 150.18, 150.22, 168.01, 168.79, 170.21. ms: m/z 1020(MH^+), 978, 962, 847. Anal. Calcd. for $C_{26}H_{29}N_3O_{11}BrI_3$: C, 30.62; H, 2.87; N, 4.12; Br, 7.83; I, 37.36. Found : C, 30.60; H, 2.75; N, 4.12; Br, 7.75; I, 37.10.

N,N'-bis[2,3-bis(acetyloxy)propyl]-5-(2-oxo-1-piperidinyl)-2,4,6-triiodo-1,3-benzene-dicarboxamide (37b). Starting from **32b** (23.8 g, 24 mmole), N,N-dimethylacetamide (200 mL) and potassium carbonate (16.5 g, 0.12 mole) and employing procedure B for 4 h and workup as described for **35b**, followed by crystallization from acetone-hexanes, **37b** (20.1 g, yield 87%) was obtained as white needles. mp: 130-34°C. hplc: t_R 5.8 min in acetonitrile-water (45:55) at 0.5 mL/min. ir: 1742, 1665, 1547, 1372, 1236, 1049 cm^{-1}. ^{1}H-nmr: δ 2.05 (m, 4H), 2.11 (s, 0.45H, residual acetone), 2.16 (s, 6H), 2.20 (s, 6H), 2.46 (m, 2H), 3.7 (M, 4H), 4.29 (m, 2H), 4.36 (m, 2H), 5.24 (br s, 2H). ^{13}C-nmr: δ 20.4, 22.9, 20.7, 21.1, 32.4, 39.8, 48.7, 63.2, 70.0, 88. 9, 96.7, 148.0, 150.6, 169.2, 169.3, 169.7, 170.4, 170.6. ms: m/z 956 (MH^+), 896, 854, 828, 781, 768, 739, 726, 702, 655, 642, 626. Anal. Calcd. for $C_{27}H_{32}I_3N_3O_{11}$•0.15 acetone: C, 34.20; H, 3.44; I, 39.49; N, 4.36; O, 18.51. Found : C, 34.01; H, 3.26; I, 39.19; N, 4.20.

N,N'-bis(2,3-bis-Dihydroxypropyl)-2,4,6-triiodo-5-(2-oxo-1-piperidinyl)-1,3-benzenedicarboxamide (37d). Starting from **37b** (17.2 g, 18 mmole), methanol (100 mL) and sodium methoxide in methanol (2 mL; 1.05M) and following procedure D for 7 h, **37d** (11.95 g, yield 85%) was obtained as a white solid. mp: 214-219°C. hplc: t_R 7.5 min by aminopropyl silica column in acetonitrile-water (4:1) at 1.0 mL/min. uv (acetonitrile): λ_{max} 240 nm (ε_{max} 30,100). ir: 3403, 1645, 1551, 1437, 1354, 1269 cm^{-1}.

^{1}H-nmr (dimethylsulfoxide -d_6): δ 1.98 (m, 2H), 2.1 (m, 2H), 2.49 (m, 2H), 3.23 (m, 2H), 3.48 (br s, 4H), 3.79 (br s, 2H), 4.58 (m, 2H), 4.90 (m, 2H), 8.25 (br d, 0.33H, NH), 8.60 (br d, 1.67H, NH). ^{13}C-nmr (dimethylsulfoxide -d_6): 20.5, 22.8, , 32.4, 42.5, 42.7, 48.5, 63.9, 64.0, 69.8, 69.9, 90.9, 97.4, 98.0, 147.4, 167.6, 169.4. ms: m/z **788** (MH^+), 697, 662, 571. Anal. Calcd. for $C_{19}H_{24}I_3N_3O_7$: C, 28.99; H, 3.07; I, 48.37; N, 5.34; O, 14.23. Found: C, 28.73; H, 3.11; I, 48.09; N, 5.20.

Dimethyl 5-(3-bromo-2-oxo-1-piperidinyl)-2,4,6-triiodo-1,3-benzenedicarboxylate (38a). Starting from **31a** (1.2 g, 1.5 mmole), N,N-dimethylacetamide (7 mL), and potassium carbonate (1.3 g, 5.8 mmole) and employing procedure B for 30 min, a mixture resulted, which was added to iced water (80 mL). The resulting solid was filtered, dried, and crystallized from ethyl acetate to obtain **38a** (0.8 g, yield 73%) as an off-white solid. mp: 255-60 °C. tlc: *Rf* 0.23 in ethyl acetate - hexane (1:1). hplc: t_R 6.5 min in acetonitrile-water (7:3) at 0.5 mL/min. uv (acetonitrile): λ_{max} 241.4, (ε 31,860). ir: 1734, 1684.6, 1525, 1221 cm^{-1}. ^{1}H-nmr (dimethylsulfoxide -d_6): δ 2.03-2.43 (m, 4H); 3.45-3.65 (m, 2H); 3.91 (s, 6H); 4.93 (t, 1H, J = 4.0 Hz). ^{13}C-nmr (dimethylsulfoxide -d_6): δ 19.0 , 30.9, 45.9, 48.5, 53.4, 89.7, 98.1, 98.4, 146.7, 148.1, 148.3, 164.0, 167.8. ms: m/z 748,750 (bromine isotope cluster, MH^+); 716,718 (bromine isotope cluster, MH-OCH_3); 669 (MH^+-Br). Anal. Calcd. for $C_{15}H_{13}BrI_3NO_5$•0.07 H_2O. C, 24.05; H, 1.77; Br, 10.67; I, 50.82; N, 1.87; O, 10.83%. Found: C, 24.20; H, 1.51; Br, 10.68; I, 50.90; N, 1.69. H_2O (KF) 0.17% (0.07 mole).

N,N'-bis-[2,3-bis-(Acetyloxy)-1-propyl]-5-(3-bromo-2-oxo-1-piperidinyl)-2,4,6-triiodo-1,3-benzenedicarboxamide (38b). Starting from **31b** (20.65 g, 18.5 mmole), N,N-dimethylacetamide (200 mL), and potassium carbonate (20.04 g, 92.6 mmole) and employing procedure B for 4 h, a mixture resulted, which was partitioned between ethyl acetate and water, the organic layer washed with water, dried, and the solvent removed. Purification of the residue by chromatography using 10% chloroform - ethyl acetate (1:9) afforded **38b** (14.04 g, yield 73%) as a white amorphous solid. mp: 232-35 °C. tlc: *Rf* 0.21 in ethyl acetate -hexane (8:2). hplc: t_R 5.9 min by 10 cm column in acetonitrile - water (1:1) at 0.5 mL/min. uv (acetonitrile): λ_{max} 241 nm (ε 28,900). ir: 1737, 1669, 1541, 1240 cm^{-1}. ^{1}H-nmr (dimethylsulfoxide -d_6): δ 2.11 (s, 12 H), 2.16-2.56 (m, 4H), 3.44-3.64 (m, 6H), 4.29 (q, 2H), 4.36 (q, 2H), 4.98 (br q, 1H), 5.17 (m, 2H), 8.29 (m, 1H) and 9.03 (m, 1H). ^{13}C-nmr (dimethylsulfoxide -d_6): δ 19.1, 20.5, 21.0, 30.8, 38.9, 46.1, 48.6, 62.9, 69.5, 91.1, 97.2, 146.1, 150.4, 150.6, 163.6, 169.4, 169.8, 170.1. ms: m/z 1034, 1036 (MH^+), 976, 974, 932, 934, 859, 861, 768, 702, 653. Anal. Calcd. for $C_{27}H_{31}BrI_3N_3O_{11}$•0.85 H_2O (within error of KF titration): C, 30.90; H, 3.14; Br, 7.61; I, 36.28; N, 4.02; O, 18.06. Found: C, 31.23; H, 2.89; Br, 7.53; I, 35.88; N, 4.02; H_2O (KF) 1.13% (0.66 mole).

N,N'-bis[2-(Acetyloxy)-1-[(acetyloxy)methyl]ethyl]-5-(3-bromo-2-oxo-1-piperidinyl)-2,4,6-triiodo-1,3-benzenedicarboxamide (38c). Starting from **31c** (32.5 g, 29.1 mmole), N,N-dimethylacetamide (250 mL) and potassium carbonate (25.2 g, 0.12 mole) and employing procedure B for 4 h and workup as for **38b**, followed by crystallization from ethyl acetate, **38c** (23.95 g, yield 80%) was obtained as a white solid. mp: 231-233°C. tlc: R_f 0.34 in ethyl acetate -hexane (8:2). hplc: t_R 3.7 min by 10 cm column in acetonitrile-water (7:3) at 0.5 mL/min. uv (acetonitrile): λ_{max} 241 nm (ε 32,000). ir: 1734, 1672, 1542, 1243, 1048 cm^{-1}. ^{1}H-nmr (dimethylsulfoxide -d_6): δ 1.85-2.04 (m, 2H); 1.93 (s, 12H); 2.18 (m, 2H); 3.30-3.46 (m, 2H), 4.04 (d, 1H, J=5.3 Hz), 4.22 (m, 1H), 4.79 (dd, 1H), 8.68 and 8.84 (dd, 2H J=7.8 Hz). ^{13}C-nmr (dimethylsulfoxide -d_6): δ 19.1, 20.7, 30.8, 46.24, 46.9, 48.6, 62.0, 91.1, 97.2, 97.4, 146.1, 150.2, 150.4, 163.6, 168.9, 170.2. ms: m/z 1034, 1036 (MH^+), 994, 992, 976, 974, 861, 859. Anal. . Calcd. for $C_{27}H_{31}BrI_3N_3O_{11}$• 0.06 H_2O : C, 31.32; H, 3.03; Br, 7.72; I, 36.78; N, 4.06; O, 17.00. Found: C, 31.65; H, 2.96; Br, 7.78; I, 37.08; N, 3.86. H_2O, 0.10% (0.06 mole).

N,N'-bis[2,3-bis-(Acetyloxy)-1-propyl]-5-[3-bromohexahydro-2-oxo-1H-azepin-1-yl]-2,4,6-triiodo-1,3-benzenedicarboxamide (39b). Starting from **33b** (5.10 g, 4.5 mmole), N,N-dimethylacetamide (60 mL), and potassium carbonate (3.42 g, 24.8 mmole) and employing procedure B for 21 h and workup as for **38b**, followed by chromatography using ethyl acetate -hexane (3:1) **39b** (3.4g, yield 72%) was obtained as a white solid. tlc: R_f 0.21 in ethyl acetate -hexane (3:1). hplc: t_R 8.2 min in acetonitrile-water (1:1) at 1 mL/min. ir: 1740, 1669, 1541, 1235 cm^{-1}. ^{1}H-nmr (dimethylsulfoxide -d_6): δ 2.00 (br s, 14H), 2.25 (m, 4H), 3.5 (m, 6H), 4.24 (m, 4H), 5.1 (m, 3H), 8.71 (br d, 1H), 8.99 (br s, 1H). ^{13}C-nmr (dimethylsulfoxide -d_6): δ 20.6, 21.0, 25.5, 27.7, 39.2, 52.0, 53.2, 63.0, 69.5, 90.4, 96.9, 98.2, 98.4, 98.6, 150.4, 150.5, 150.6, 150.7, 150.9, 167.3, 169.6, 169.7, 169.9, 170.2. ms: m/z 1049, 1047 (bromine isotope cluster, MH^+), 990, 921, 873, 842, 667. Anal. Calcd. for $C_{28}H_{33}BrI_3N_3O_{11}$•0.20 H_2O : C, 31.98; H, 3.20; N, 4.00; Br, 7.60; I, 36.20; O, 17.03. Found: C, 32.35; H, 3.12; N, 3.87; Br, 7.60; I, 36.19; H_2O (KF) 0.34% (0.20 mole).

Dimethyl 5-[3-(acetyloxy)-2-oxo-1-pyrrolidinyl]-2,4,6-triiodo-1,3-benzenedicarboxylate (40a). Starting from **36a** (1.10 g, 1.5 mmole), silver acetate (1.0 g, 6.0 mmole), and acetic acid (15 mL) and employing procedure C for 23.5 h, **40a** (0.98 g, 91% yield) was obtained as a white foam, after chromatography using methylene chloride-ethyl acetate (25:1). TLC R_f 0.32 in methylene chloride: ethyl acetate (20:1). hplc: t_R 5.03 min by 15 cm column in acetonitrile-water (7:3). uv (acetonitrile): λ_{max} 242 nm (ε 32,000). ir (chloroform): 1735, 1712, 1524, 1231 cm^{-1}. ^{1}H-nmr: δ 2.19 (s, 3H), 2.29 (m, 1H), 2.80 (m, 1H), 3.72 (m, 2H), 3.97 (s, 3H), 3.98 (s, 3H), 5.48 (m, 1H). ^{13}C-nmr: δ 20.8, 27.0, 43.6, 53.4, 70.5, 88.40, 95.57,

96.43, 143.64, 149.02, 167.62, 168.52, 170.10. ms: m/z 714 $(MH)^+$,586. Anal. Calcd. for $C_{16}H_{14}I_3NO_7$: C, 26.95; H, 1.98; N, 1.96; O, 15.71; I, 53.40. Found: C, 27.20; H, 1.64; N, 1.86; I, 52.96.

5-[3-(Acetyloxy)-2-oxo-1-pyrrolidinyl]-N,N'-bis-[2,3-bis(acetyloxy)-1-propyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (40b). Starting from **36b** (53.42 g, 52.4 mmole), silver acetate [(I) 35.0 g, 0.21 mole; (II) 8.74 g, 52.4 mmole], and acetic acid (520 mL) and employing procedure C for 44 h, **40b** (38.4 g, yield 73%) was obtained as an off-white foam, after chromatography using ethyl acetate-methylene chloride. tlc: *Rf* 0.16 in ethyl acetate-methylene chloride (2:1). hplc: t_R 13.6 min by isocratic elution with acetonitrile-water (2:8) followed by gradient elution using 20-70% acetonitrile in water over 13 minutes at 1.0 mL/min; uv (acetonitrile): λ_{max} 243 nm (ε 28,800). ir: 1732, 1667, 1541, 1426, 1372, 1241, 1049 cm^{-1}. ^{1}H-nmr (dimethylsulfoxide -d_6): δ 2.03 (s, 12H); 2.14 (s, 3H); 2.20 and 2.70 (m, 2H); 3.50 (m, 1H); 3.50 (m, 4H); 3.70 (m, 1H); 4.24 (m, 4H); 5.09 (br s, 1H); 5.43 (t, 1H); 8.49 and 8.96 (m, 2H). ^{13}C-nmr (dimethylsulfoxide -d_6): δ 20.61, 21.06, 26.48, 39.81, 43.38, 63.00, 69.52, 70.17, 92.03, 92.27, 92.51, 97.04, 97.25, 97.45, 98.01, 98.22, 98.27, 98.43, 142.94, 150.40, 150.46 , 168.02, 169.39, 169.66, 169.91, 170.21. ms: m/z 1000(MH^+), 958, 940, 874. Anal. Calcd. for $C_{28}H_{32}N_3O_{13}I_3$: C, 33.65; H, 3.23; N, 4.21; I, 38.10; O, 20.82. Found: C, 33.73; H, 3.07; N, 4.23; I, 37.77.

N,N' - Bis [2-(Acetyloxy)-1-[(acetyloxy)methyl] - ethyl] - 5- [3 - (acetyloxy) - 2 - oxo - 1 - pyrrolidinyl] - 2,4,6 - triiodo - 1,3 - benzenedicarboxamide (40c). Starting from **36c** (77.5 g, 76 mmole), silver acetate (65.5 g, 0.39 mole) and acetic acid (760 mL) and employing procedure C for 34 h, **40c** (46.93 g 62% yield) was obtained as a white solid, after chromatography using ethyl acetate-methylene chloride. mp: 140-142 °C. tlc: *Rf* 0.35; ethyl acetate methylene-chloride (4:1). hplc: t_R 12.32 min by isocratic elution with 20% acetonitrile-water for 2 min, then ramp to 60% acetonitrile-water over 15 min and hold at 60% acetonitrile-water for 10 min at 1.0 mL/min. uv (methanol): λ_{max} 243.4 nm, (ε 29,300). ir (Diffuse Reflectance): 3321, 3264, 3079, 2955, 1736, 1669, 1539, 1236 cm^{-1}. ^{1}H-nmr: δ 2.06 and 2.08 (s, 1.0/0.82 ratio, 12H), 2.18 (s, 3H), 2.25 (m, 1H), 2.78 (m, 1H), 3.75 (m, 2H), 4.28 (br s, 8H), 4.61 (br s, 2H), 5.45 (m, 1H), 6.40 (m, 0.5H, NH), 7.15 (br m, 1.2H, NH), 7.40 (br m, 0.3H, NH). ^{13}C-nmr: δ 20.72, 26.64, 43.55, 47.45, 47.62, 47.82, 62.14, 70.39, 89.99, 96.15, 96.42, 96.73, 97.01, 143.14, 143.55, 149.70, 149.78, 150.07, 150.23, 168.38, 168.49, 169.77, 169.95, 170.05, 170.49, 170.55, 170.68. ms: m/z 1000(MH^+), 958, 940, 898, 825, 783. Anal. Calcd. for $C_{28}H_{32}N_3O_{13}I_3$: C, 33.65; H, 3.23; N, 4.21; I, 38.10. Found: C, 33.75; H, 3.30; N, 4.27; I, 37.83.

5-[3-(Acetyloxy)-hexahydro-2-oxo-1H-azepin-1-yl]-N,N'-bis[2,3-bis(acetyloxy)-1-propyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (41b). Starting from **39b** (3.3g, 3.1 mmole), silver acetate (2.6 g, 15.5 mmole), acetic acid (30 mL), and acetic anhydride (0.32 g, 3.1 mmole) and employing procedure C for 5.5 days, **41b** (2.04 g, yield 63%) was obtained as a white solid, after chromatography using a gradient of ethyl acetate-hexane (7:3) to ethyl acetate. tlc: *Rf* 0.30 in ethyl acetate -hexane (85:15). hplc: t_R 5.45 min in acetonitrile-water(1:1) at 1.0 mL/min. ir: 1742, 1669, 1541, 1235 cm^{-1}. ^{1}H-nmr (dimethylsulfoxide -d_6): δ 1.90 (m, 4H), 2.00 (s, 15H), 2.22 (m, 2H), 3.47 (m, 6H), 4.21 (m, 4H), 5.08 (br s, 2H), 5.45 (d, 1H), 8.70 (m, 1H), 8.91 (br s, 1H). ^{13}C-nmr (dimethylsulfoxide -d_6): δ 20.6, 20.7, 21.0, 26.2, 27.8, 27.9, 39.2, 52.1, 63.0, 69.5, 73.0, 90.5, 97.2, 99.0, 150.2, 150.3, 150.5, 150.6, 150.7, 150.9, 168.3, 168.5, 169.90, 169.7, 169.8, 169.9, 170.2. ms: m/z 1028 (MH^+), 968, 900. Anal. Calcd. for $C_{30}H_{36}I_3N_3O_{13}$ •0.26 H_2O: C, 34.91; H, 3.57; I, 36.98; N, 4.07; O, 20.56. Found: C, 34.94; H, 3.49; I, 36.48; N, 3.76; H_2O (KF) 0.46% (0.26 mole).

Dimethyl 5-(3-hydroxy-2-oxo-1-pyrrolidinyl)-2,4,6-triiodo-1,3-benzenedicarboxylate (42a). Starting from **40a** (0.5 g, 0.69 mmole), and sodium methoxide (8 mg, 0.15 mmole) and methanol (5 mL) and employing procedure D for 40 min, **42a** (0.25 g, yield 54%) was obtained as pale pink crystals, after crystallization from ethyl acetate - methanol. mp: 266-267 °C (compound changes form substantially at 240 °C). tlc: *Rf* 0.20 in ethyl acetate:hexane (1:1). hplc: t_R 4.02 min in acetonitrile-water (7:3) at 0.50 mL/min. uv (acetonitrile): λ_{max} 242 nm (ε 30,100). ir (Nujol): 3350, 1732, 1694, 1530, 1455, 1233 cm^{-1}. ^{1}H-nmr (dimethylsulfoxide -d_6): δ 2.044 (m, 1H), 2.55 (m, 1H), 3.56 (m, 2H), 3.92 (s, 3H), 3.93 (s, 3H), 4.26 (m, 1H), 5.92 (d, 1H). ^{13}C-nmr (dimethylsulfoxide -d_6): δ 29.10, 42.98, 53.38, 68.96, 90.13, 98.25, 99.43, 144.17, 147.91, 147.98, 167.82, 172.82. ms: m/z 688.6 $(M+NH_4)^+$, 562.7 ($M+NH_4$ - I). Anal. Calcd. for $C_{14}H_{12}I_3NO_6$: C, 25.06; H, 1.80; N, 2.09; O, 14.3; I, 56.74. Found : C, 25.11; H, 1.64; N, 1.96; I, 56.59.

N,N'-bis(bis-2,3-Dihydroxypropyl)-5-(3-hydroxy-2-oxo-1-pyrrolidinyl)-2,4,6-triiodo-1,3-benzenedicarboxamide (42d). Starting from **40b** (37.1 g, 37.2 mmole), methanol (300 mL) and sodium methoxide in methanol (7.5 mL; 0.66 M) and employing procedure D for 3 h, **42d** (25.9 g, yield 89%) was obtained as a white foam, after chromatography. A small amount was crystallized from hot absolute ethanol to obtain a white crystalline solid. mp: 165 - 250°C (dec). tlc: *Rf* 0.21 in methylene chloride -methanol (7:3). hplc: t_R 14.7 min by aminopropyl silica in acetonitrile-water (8:2) at 1.0 mL/min. uv (methanol): λ_{max} 243 nm (ε = 30,1000). ir: 1694, 1645, 1556, 1430, 1269, 1115 cm^{-1}. ^{1}H-nmr (dimethylsulfoxide -d_6): δ 2.13 (m, 1H); 2.66 (m, 1H,); 3.26 and 3.52 (m, 4H); 3.52 (m, 1H); 3.7 (m, 1H); 3.79 (m, 2H); 4.34 (m, 1H); 4.61 (br s, 2H); 4.82 and 4.90 (m, 2H); 5.96 (m, 1H,); 8.32, 8.58, and 8.70 (m, 2H). ^{13}C-nmr (dimethylsulfoxide -d_6): δ 29.25, 42.69, 43.17, 64.05, 69.23, 70.04, 92.09, 97.15, 97.49, 97.56, 98.61, 143.46, 150.56, 150.61, 169.37, 169.48,

172.73, 172.76. ms: m/z 789.9(MH^+), 698.9, 664.1. Anal. Calcd. for $C_{18}H_{22}N_3O_8I_3 \bullet 0.3\ H_2O$: C, 27.40; H, 2.81; N, 5.33; I, 48.25; O, 16.22. Found: C, 27.47; H, 3.03; N, 5.11; I, 48.10; H_2O (KF) 0.7% (0.3 mole).

N,N'-bis-[2-Hydroxy-1-(hydroxy)methyl-ethyl]-5-(3-hydroxy-2-oxo-1-pyrrolidinyl)-2,4,6-triiodo-1,3-benzenedicarboxamide (42e). Starting from **40c** (40.0 g , 40.0 mmole), methanol (320 mL) and sodium methoxide in methanol (7.5 mL; 6.3 M) and employing procedure D for 5.0 h, **42e** (27.19 g, yield 86%) was obtained as a white solid, after chromatography. tlc: Rf 0.33 in chloroform - methanol (7:3). hplc: t_R, 11.77 min by 15 cm x 4 mm aminopropyl silica column in acetonitrile-water (4:1) at 1.0 mL/min. uv (acetonitrile): λ_{max} 243.2 nm, (ε 28,700). ir: 3414, 3270, 1699, 1650, 1542 cm^{-1}. ^{1}H-nmr (dimethylsulfoxide-d_6): δ 2.03 (m, 1H), 2.55 (m, 1H), 3.40-3.78 (overlapping m, 6H), 3.83 (br s, 2H), 4.25 (m, 1H), 4.55 (br s, 3H), 4.65 (br s, 1H), 5.87 (d, J=4 Hz, 1H), 7.78 (m, 0.4H, NH), 8.25 and 8.35 (m, 1.6H, NH). ^{13}C-nmr (dimethylsulfoxide-d_6): 29.09, 42.97, 52.98, 53.22, 58.91, 59.20 and 59.28, 69.10, 92.01, 96.99, 97.44, 98.11, 98.58, 143.29, 150.30, 150.36 and 150.41, 168.64, 168.84, 172.52, 172.57. ms: m/z 790(MH^+), 772, 699, 664. Anal. Calcd. for $C_{18}H_{22}N_3O_8I_3 \bullet 0.23\ H_2O$: C, 27.25; H, 2.85; N, 5.30; I, 47.99. Found: C, 27.13; H, 3.08; N, 5.33; I, 47.94; H_2O, 0.52% (0.23 mole) (KF).

N,N'-bis[2,3-Dihydroxy-1-propyl]-5-[hexahydro-3-hydroxy-2-oxo-1H-azepin-1-yl]-2,4,6-triiodo-1,3-benzenedicarboxamide (43d). Starting from **41b** (2.0 g, 1.95 mmole), methanol (10 mL), sodium methoxide in methanol (0.2 mL; 0.5M) and employing procedure D for 3h, **43d** (1.1 g, yield 70%) was obtained as a white solid. mp: 263-265 °C. tlc: Rf 0.42 in chloroform-methanol (7:3). hplc: t_R 7.2 min by aminopropyl silica column. uv (water:) λ_{max} 244 (ε 26,700). ir: 3393, 1651, 1553, 1267 cm^{-1}. ^{1}H-nmr: (dimethylsulfoxide-d_6): δ 1.90 (br m, 4H), 2.50 (br m, 2H), 3.39 (br m, 10H), 3.95 (t, 1H), 4.36 (br s, 2H), 4.53 (m, 2H), 4.75 (m, 3H), 8.05-8.55 (4 br s, 2H). ^{13}C-nmr (dimethylsulfoxide-d_6) δ 27.6, 28.9, 33.0, 43.7, 53.0, 65.1, 71.1, 72.0, 91.8, 99.0, 151.6, 151.7, 151.9, 152.0, 170.6, 170.7, 175.1, 175.2. ms: m/z 895 (M+ matrix dimethylsulfoxide $^+$), 818 (MH^+), 692. Anal. Calcd. for $C_{20}H_{26}I_3N_3O_8 \bullet 0.96\ H_2O$: C, 28.78; H, 3.37; I, 45.62; N, 5.04; O, 17.19. Found: C, 28.93; H, 3.12; I, 45.48; N, 4.89; H_2O (KF) 2.08 % (0.96 mole).

Dimethyl 5-[[dihydro-2(3H)-furanylidene]-amino]-2,4,6-triiodo-1,3-benzenedicarboxylate (44a). The mother liquor from the crystallization of **35a** was chromatographed using chloroform - ethyl acetate (50:1) to provide **44a** as a yellow powder (0.45 g, 6.9% yield). uv (acetonitrile): λ_{max} 239 (ε_{max} 31,062). ir: 2951, 1721, 1709, 1692, 1337, 1219 cm^{-1}. ^{1}H-nmr (dimethylsulfoxide-d_6): δ 2.20 (m, 2.37H), 2.81 (m, 1.52H), 3.88 (s, 6H), 4.36 (br m, 2.10H). ^{13}C-nmr (dimethylsulfoxide-d_6): δ 22.9, 27.8, 28.9, 53.0, 71.9, 80.5, 88.6, 146.8,

166.7, 168.1. ms: m/z 655 (MH^+), 530, 404. Anal. Calcd. for $C_{14}H_{12}I_3NO_5$: C, 25.67; H, 1.85; I, 58.13; N 2.14. Found: C, 25.83; H, 1.76; I, 58.46; N, 2.06.

N,N'-bis[2,3-bis(Acetyloxy)-1-propyl]]-5-[[dihydro-2(3H)-furanylidene]-amino]-2,4,6-triiodo-1,3-benzenedicarboxamide (44b). Fractions 1-56 in the chromatographic isolation of **35b** were freed of solven to obtain **44b**. hplc: t_R 12.64 min in acetonitrile-water (3:7); isocratic for 2 min, then ramp to acetonitrile water (3:2) over 15 min and hold for 8 min at 1.0 mL/min. ir: 2935, 1736, 1662, 1242 cm^{-1}. ^{1}H-nm (dimethylsulfoxide-d_6): δ 2.03 (s, 12H), 2.16 (m, 2.11H), 2.76 (br m, 1.22H), 3.43 (m, 3.29H), 4.15 (m, 2H) 4.25 (m, 3.76 H), 5.08 (br m, 2H), 8.45 (br d, 0.38 H, NH), 8.70 (br m, 1.62 H, NH). ^{13}C-nm (dimethylsulfoxide-d_6): δ 20.6, 21.1, 22.9, 29.0, 38.8, 63.0, 69.5, 71.1, 72.0, 82.5, 88.8, 149.0, 153.2, 166.0 169.9, 170.2. ms: m/z 942 (MH^+), 882, 816,767, 690, 641, 515. Anal. Calcd. for $C_{26}H_{30}I_3N_3O_{11}$: C, 33.18; H, 3.21; I, 40.45; N, 4.47; O, 18.70. Found: C, 33.52; H, 3.41; I, 40.51; N, 4.13.

N,N'-bis[2,3-bis(Acetyloxy)-1-propyl]]-5-[2-oxo-1-(Δ-3,4)-pyrrolidinyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (45b). A mixture of **36b** (3.66 g, 3.59 mmole), fused sodium acetate (3.66 g, 44.6 mmole), and N,N-dimethylacetamide (20 mL) was heated at 145°C for 1.5 h, the mixture cooled to ambient temperature, ethyl acetate (25 mL) added, the salts filtered off, and the solvents removed. The residue was partitioned between ethyl acetate (200 mL) and brine (150 mL). The organic layer was dried, the solvent removed, and the residue purified by chromatography using a gradient elution of methylene chloride - ethyl acetate (2.5:1 to 4:1) to obtain **40b** (0.91 g, 25% yield) and **45b** (1.18 g, 34% yield; purity 92%; contaminated with 7% of **40b**). **45b** had the following properties: tlc: Rf 0.12 in methylene chloride-ethyl acetate (1:2.5). hplc: t_R 10.96 min in acetonitrile-water (3:7); isocratic for 2 min, then ramp to acetonitrile-water (6:4) in 15 min and hold 6 min at 1.0 mL/min (t_R for **40** 12.73 min.); ^{1}H-nmr: δ 2.12 (s, 12H), 3.75 (2 overlapping br s, 4H), 4.35 (m, 6H), 5.28 (br s, 2H), 6.30 (br d, J=7Hz, 0.9H), 7.32 (br d, overlapped by residual chloroform). The fractional number of protons is due to the contaminant **40b**.

N,N'-Bis-[2-Acetyloxy-1-[acetyloxymethyl]-ethyl-5-[2-oxo-1-(Δ-3,4)-pyrrolidinyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (45c). A mixture of **36c** (10.20 g, 10.0 mole), fused sodium acetate (10.0 g, 0.12 mole), and N,N-dimethylacetamide (85 mL) was heated at 148°C for 1.5 h. The workup described for **45b** was followed. The pooling of respective fractions gave **40c** (1.32 g, 13% yield) and **45c** (0.95 g, 10% yield, 88% purity; contaminated with 8.9% of **40c** and 1.25% of unknowns). **45c** had the following properties: tlc: Rf 0.21 in methylene chloride - ethyl acetate (1:2.5). hplc: t_R 6.49 min in 0.02M aqueous ammonium acetate-acetonitrile (3:2) at 0.5 mL/min (t_R for **40c** 8.12 min). ^{1}H-nmr (dimethylsulfoxide-d_6): δ 2.15 (s, 12H), 4.35

(m, 12H), 6.30 (d, J=7Hz, 1H), 7.52 (d, J=7Hz, 1H), 8.8 - 9.0 (2dd, J=8 Hz, 2H). ^{13}C-nmr (dimethylsulfoxide-d_6): δ 20.8, 46.8, 51.9, 62.1, 91.8, 98.9, 99.0, 127.0, 143.3, 146.2, 149.9, 168.9, 170.3. lc/ms (electrospray, ammonium acetate): 1017 ($M+NH_4^+$), 1000 (MH^+), 891.

ACKNOWLEDGMENT

We wish to acknowledge Dr. M. Tweedle for encouragement throughout this work, Dr. K. Kumar, Ms. M. Fernandez and Mr. Z. Ugwuneri for physical measurements, and Mr. P. Wedeking for biological studies. We also thank the BMSPRI Analytical Division for spectral data and elemental analysis determinations.

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(*Received in USA* 7 *May* 1996; *revised* 8 *July* 1996; *accepted* 9 *July* 1996)