Heterocyclic Nonionic X-ray Contrast Agents. 3. The Synthesis of 5-[4-(Hydroxymethyl)-2-oxo-3-oxazolidinyl]-2,4,6-triiodo-1,3-benzenedicarboxamide Derivatives

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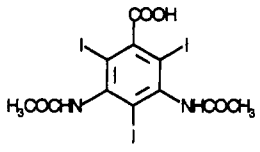
Received October 4, 1993®

The syntheses of 2,4,6-triiodo-1,3-benzenedicarboxamide analogs, **12c**, **12e**, and **17c**, of interest as X-ray diagnostic agents and in which the 5 position is linked to the N atom of a 4-(hydroxymethyl)-oxazolidin-2-one moiety, are described. The heterocycle was built from suitably protected 5-amino-2,4,6-triiodo-1,3-benzenedicarboxylic acid derivatives by a three-step procedure consisting of (1) phosgene treatment to obtain the corresponding isocyanates, (2) phenylmercuric chloride-catalyzed addition of glycidol (**10**) resulting in glycidyl carbamates, and (3) pyridine-catalyzed intramolecular N-alkylation, followed by deprotection, to obtain the oxazolidin-2-ones. The intramolecular N-alkylation reaction was highly regioselective and was not appreciably accompanied by *O*-alkylation products under the experimental conditions employed. The two carboxamide nitrogen atoms in the intermediates and end products carry either 2,3-dihydroxypropyl or 1,3-dihydroxypropyl residues. These highly congested benzenoid compounds exhibited interesting NMR spectral features due to atropisomerism arising from hindrance to free rotation about the three single bonds that link the aromatic moiety to the N-containing functionalities.

Introduction

The design, synthesis, and development of new and improved derivatives of 2,4,6-triiodo-1,3-benzenedicarboxamide, which are routinely employed[1] as contrast agents for imaging soft tissues using X-rays, are of importance in diagnostic radiology for increased safety, efficiency, and patient comfort. In parts I and II[2] of this series we dwelt at length on design considerations that led us to explore the concept of heterocyclic nonionic iodinated contrast media (NICM). To briefly recapitulate, the hyperosmolality of the highly concentrated aqueous solutions of the ionic agents **1** and **2** is implicated in the high levels of adverse drug reactions[3] encountered in their clinical use. To counter this, nonionic iodinated contrast agents (NICM), such as iopamidol (**3**)[4] and iohexol[5] (**4**), possessing lower osmolality were developed. In attempting the current work, it was our intention to further improve some of the design features of NICM.

In the case of iohexol (**4**), the observed hydrolytic instability of the ArN–(CO) bond leading to the corresponding aniline, during autoclaving procedures or during storage of the injectable solutions, is thought to arise from the anchimeric assistance to the cleavage of the amide bond provided by the neighboring hydroxyl groups. The poor tolerance of the resulting anilines is incompatible with radiological applications. Though this problem has been alleviated[6] by imaginative formulation techniques, there is still a need to develop more stable nonionic contrast agents possessing better hydrolytic stability characteristics. A second improvement that we desired is the further lowering of the osmolality of the injectable NICM solutions.



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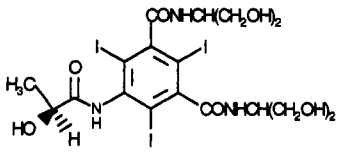

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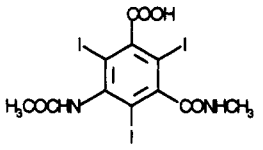

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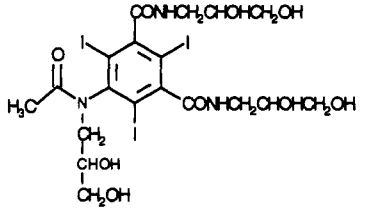

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To achieve these improvements we initially proposed the synthesis of NICM candidates of the structural class **12** (Scheme 2) based on the oxazolidin-2-one moiety. Structures of this type could be expected to provide highly stable molecules at physiological pH ranges, since destabilizing structural features are absent. It was also our premise that these *N*-[4-(hydroxymethyl)oxazolidin-2-one]-substituted triiodobenzenoids could be more amphiphilic than iopamidol (**3**) or iohexol (**4**) leading to greater self-association in aqueous solution, which would in turn lead to lower osmolality. The increased amphiphilicity could arise from increased rigidity due to α-branched heterocyclization and the presence of sterically congested

® Abstract published in *Advance ACS Abstracts*, February 1, 1994.

(1) (a) Hoey, G. B.; Weight, P.; Ranks, R. D., Jr. Organic Iodine Compounds as X-Ray Contrast Media. In Knoefel, P. K., Ed. Radiocontrast Agents; Pergamon Press: New York, 1971; Sect. 76, Vol.1, pp 23–131. (b) Hoey, G. B.; Smith, K. R. Chemistry of X-Ray Contrast Media. In Sovak, M., Ed. Radiocontrast Agents; Springer-Verlag: Basel, 1984; pp 23–125.

(2) For part I see Ranganathan, R. S.; Arunachalam, T.; Diamantidis, G.; Duncan, L.; Emswiler, J.; Marinelli, E.; Neubeck, R.; Pillai, R.; Wedeking, P.; Tweedle, M. F. *Inv. Radiol.* **1991**, *26*, S156. Part II manuscript in preparation.

(3) Katayama, H. Report of the Japanese Committee on the Safety of Contrast Media. A scientific poster session presented at the Radiological Society of North America Meeting, November, 1988.

(4) Felder, E. *Invest. Radiol.* **1984**, *19*, S164.

(5) Haavaldsen, J.; Nordal, V.; Kelly, M. *Acta. Pharm. Suec.* **1983**, *20*, 219.

(6) Rakli, F. B.; Kelly, M. J. U.S. Patent 4,278,654, July 14, 1981. See also Sovak, M.; Foster, S. J. Eur. Pat. Appl. EP 278,674, August 17, 1988 (*Chem. Abstr.* **1989**, *111*, 12524x).

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hydrophobic structural features that mask the polar nature of the hydroxymethyl group on the heterocycle.

In designing the rest of the molecule, we decided to stay with the 2,3-dihydroxypropyl or the 1,3-dihydroxypropyl residues as the carboxamide N-substituents. These two moieties have proven to be the mainstay of NICM molecules, since they offer a viable compromise among the conflicting demands of high water solubility, high iodine content, low viscosity, and low osmolality.

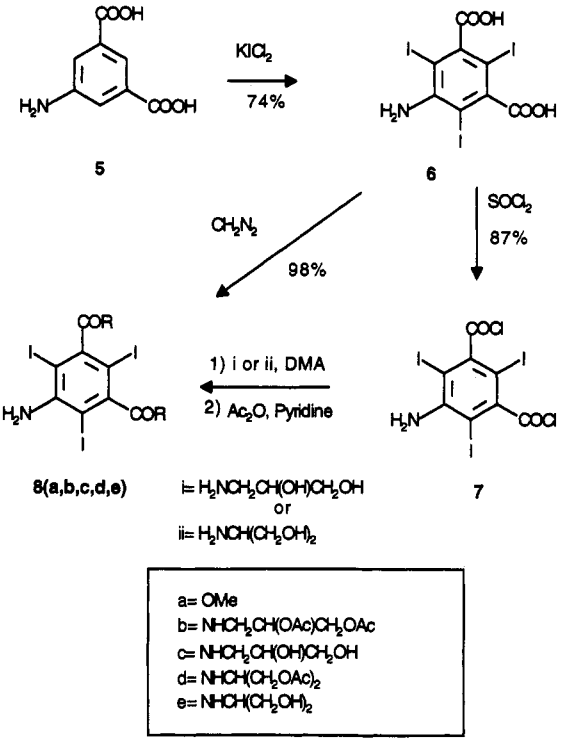
Another crucial property influencing water solubility has been recognized[1b] to be the presence of elements of asymmetry in the molecule. It has also been observed that the racemate and the enantiomeric forms of a chiral molecule may possess vastly different water solubility properties. A poignant example is provided by Iopamidol,[4] the S enantiomer of which has a water solubility of 90%, whereas the corresponding racemate exhibits a low water solubility of only 16%. In light of this, we were inclined to make some of the proposed analogs in their optically active form, should their racemic forms show poor water solubility.

It may be noted that in structure (12) the oxazolidine framework bears an α-branched hydroxymethyl group at carbon 4'. In view of the highly congested nature of the triiodobenzene moiety, it has not been possible to make such α-branched substitutions by intermolecular N-alkylation processes. We reasoned that α-branched analogs of structural class 12 may be accessible by the intramolecular delivery of a nucleophilic nitrogen atom on a suitably functionalized electrophilic moiety, such as an epoxy function, in the same molecule. Our reasoning in this regard was heavily influenced by the reported[7] conversion of glycidyl carbamates into the corresponding oxazolidin-2-ones in high yields. Our successful effort in extending prior knowledge in this area to the synthesis of the oxazolidin-2-one-based heterocyclic NICM congeners by this intramolecular cyclization methodology is described in this paper.

Results and Discussion

The starting materials needed for this study were prepared as shown in Scheme 1. The aniline **5** was iodinated according to methods similar to published procedures[8] to obtain the triiodinated bis-acid **6**. Diazomethane esterification of **6** in a mixture of methanol and ether afforded the dimethyl ester **8a** in 98% yield. Chlorination of the bis-acid **6** with purified thionyl chloride gave the previously described[9] bis-chloride **7**, which was converted into the bis-amides **8b** or **8d** by reaction with 1-amino-2,3-propanediol or with 2-amino-1,3-propanediol, respectively, in dimethylacetamide (DMA), followed by *O*-acetylation[10] with acetic anhydride in pyridine. This selective acetylation was possible because of the weak nucleophilicity of the 5-amino group in compounds **8c** and **8e** under the conditions employed.

Scheme 1



Some of the features of the ^{1}H-NMR spectrum of the compounds **8b** and **8d** warrant comment. Compound **8b** exhibited a complex multiplet pattern in the region δ 3.2–3.6, assignable to the methylene protons attached to the carboxamido N-atoms of the isophthalamide function. The complexity of this signal could be attributed to the adjacent asymmetric center, to vicinal coupling to the two neighboring protons, and also to the contributions from the various atropisomers expected, because of restriction to free rotation around the Ar–(CO) and (CO)–N bonds in the molecule. Another notable feature in the spectrum was the presence of two quartets at δ 8.67 and 8.4, in the ratio 83:17, assignable to the NH protons of the C(O)NH groups. While the quartet nature of the peaks is due to unequal spin–spin coupling to the protons of the adjacent methylene group, the presence of a pair of quartets can be ascribed to the existence of the molecule as a mixture of the *syn* and *anti* forms in the ratio 83:17, due to the lack of free rotation around the Ar–(CO) bonds. These conclusions are partly based on the published study[11] of the atropisomerism exhibited by 2,4,6- triiodoisophthalamide derivatives. The ^{1}H-NMR spectrum of the serinol derivative **8d** had similar features with the ratio of the *syn* and *anti* forms being 6.75:1.0 based on the pair of doublets at δ 8.35 and 8.72. Further, in conjunction with the ^{13}C-NMR spectrum, it could be surmised that **8d** probably exists preponderantly in either the *E* or the *Z* form, that are possible due to the partial double bond character of the amide bonds.

Synthesis of the Oxazolidine-2-one Derivatives 12. Our synthetic approach to the oxazolidin-2-one derivatives **12** is shown in Scheme 2. Initially we carried out a model study on the dimethyl ester **8a**, which is a simpler system allowing us to explore the ramifications of the ring closure process. Amino-dehalogenation of the dimethyl ester **8a** by treatment with phosgene in dioxane/toluene solution

(7) (a) Farrissay, W. J., Jr.; Nashu, A. M. *J. Heterocycl. Chem.* **1970**, *7*, 331. (b) Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109. (c) Roush, W. R.; Adam, M. A. *J. Org. Chem.* **1985**, *50*, 3752. (d) Juliana, R.; Herzig, T.; Bernet, B.; Vasella, A. *Helv. Chim. Acta.* **1986**, *69*, 368. (e) Rama Rao, A. V.; Murali Dhar, T. G.; Chakraborty, T. K.; Gurjar, M. K. *Tetrahedron Lett.* **1988**, *29*(17), 2069.

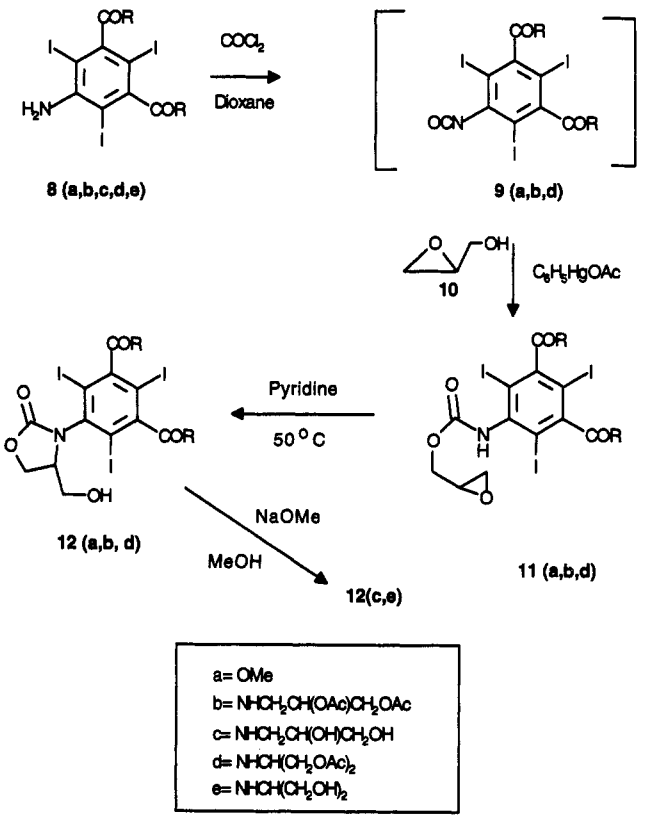
(8) Wallingford, V. H.; Decker, H. G.; Kruty, M. *J. Am. Chem. Soc.* **1952**, *74*, 4365.

(9) Felder, E.; Vitale, R. S.; Pitre, D. E. Swiss 608,189, Dec 29, 1978 (*Chem. Abstr.* **1979**, *90*: 142162m).

(10) Lin, Y. Eur. Pat. Appl. EP 83,964, Jan 11, 1982 (*Chem. Abstr.* **1983**, *99*: 212293s).

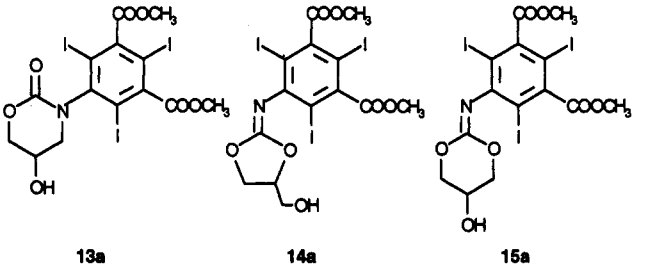
(11) Bradamante, S.; Vittadini, G. *Mag. Reson. Chem.* **1987**, *25*, 283.

Scheme 2



at 60 °C over a period of 15 h resulted in a smooth conversion into the corresponding isocyanate **9a**, detected as the corresponding methyl carbamate. Similar triiodophenyl isocyanates have earlier been described.[12] Initial attempts to add glycidol (**10**) to the crude isocyanate **9a** in the absence of a catalyst were not successful. However, in the presence of phenylmercuric acetate[7a] in dioxane, the addition went to completion at room temperature during 4 h, affording the glycidyl carbamate **11a** in 81% yield. In the ^{1}H-NMR spectrum of **11a**, the NH proton occurred as two singlets in the ratio 3:1. The same ratio was found for the resonances assignable to one of the methylene protons of the glycidyl moiety. In analogy to a published report[11] on related derivatives, we ascribe this to the presence of *endo* and *exo* isomers in the ratio 3:1, respectively, arising from restricted rotation around the carbamate N–(CO) bond.

When a pyridine solution of the oxiranylmethyl carbamate **11a** was heated at 50 °C for 2 h, it underwent a clean conversion to a more-polar major product, which constituted approximately 90% of the product mixture by TLC analysis, with 5% of starting material remaining unreacted. The crude mixture was purified by silica gel column chromatography to obtain the major product in 74% isolated yield. In the ^{1}H-NMR spectrum of the product, resonances due to the NH proton and the three oxiranyl protons were missing, leading to the postulation of plausible heterocyclic structures **12a**/**13a** or **14a**/**15a**, that could be expected by intramolecular N or O participative ring closures, respectively. A narrowing down among these possibilities was possible when we noticed that the hydroxy proton was present as a triplet, strongly suggestive of the presence of a hydroxymethyl group, which allowed us to rule out structures **13a** and **15a**. This observation is in full conformity with the reported[13] preference for the 5-exo-tet process over the 6-exo-tet process.



A choice between structures **12a** and **14a** was possible based on ^{13}C-NMR spectral data. There was a signal at 59.40 ppm which was assignable to the carbon atom of a NCH(sp^3) functionality, that is present only in the oxazolidin-2-one structure **12a**, based on published[14] data for similar derivatives. The absence of a signal around 85 ppm expected[15] for the OCH(sp^3) carbon atom precluded consideration of the iminocarbonate structure **14a**. The assignment of structure **12a** is also fully supported by the rest of the spectral and analytical data for the major isolated product. This observed preference for N-participation over O-participation during the ring closure reactions of carboxamides under basic conditions, as is obtained by the use of pyridine as the solvent, is well documented.[7,16] It is also known[7c] that O-participative ring closures may be favored under acidic conditions.

It may be noteworthy that it has so far not been possible to synthesize 5-*N*-alkyl- substituted 2,4,6-triiodo-1,3-benzenedicarboxamide derivatives in which the α position of the alkyl group was branched using intermolecular alkylation approaches on secondary halides or sulfonates. In view of the fact that the 5 nitrogen atom is poorly nucleophilic, because of steric congestion offered by the two flanking ortho-iodine atoms, this lack of reactivity is understandable. We have overcome this obstacle by resorting to an intramolecular alkylative strategy to create α-branched alkyl-substituted 5-amino-triiodobenzenoids represented by structure **12**.

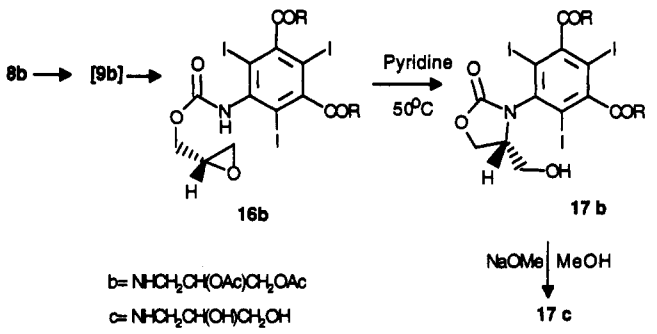
The chemistry delineated by employing the dimethyl esters as model compounds was next applied to the bisamides **8b** and **8d** with comparable results. Aminodehalogenation of **8b** and **8d** with phosgene furnished the corresponding isocyanates **9b** and **9d** which underwent smooth addition of glycidol (**10**) in the presence of phenylmercuric acetate affording the glycidyl carbamates **11b** and **11d**, in 76 and 75% yields, respectively. In the case of **9b**, the addition reaction was also performed with (*S*)-glycidol under the same conditions to afford the optically active glycidyl carbamate **16b** (Scheme III).

As in the case of **11a**, the ^{1}H-NMR spectrum of the glycidyl carbamates **11b**, **11d**, and **16b** revealed that they were mixtures of *exo* and *endo* isomers due to restricted rotation around the amide linkage of the Ar–NH–C(O)O moiety. The ratios of these two isomers were 8:2 and 9:1 in the compounds **11b** and **11d**, respectively. Again on

(12) Smitz, K. R. Ger. Offen. 2,541,491, Apr 15, 1976 (*Chem. Abstr.* **1976**, *85*: 63296b).

(13) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
(14) Knapp, S.; Levorse, A. *J. Org. Chem.* **1988**, *53*, 4006.
(15) (a) Barbaro, G.; Battaglia, A.; Giorgianni, A. P. *J. Org. Chem.* **1988**, *53*, 5501. (b) Evans, R. D.; Magee, J. W.; Schauble, J. H. *Synthesis* **1988**, 862.
(16) Smith, P. A. S. In *Open Chain Nitrogen Compounds*; Benjamin: New York, 1965; Vol. 1, pp 145–6.

Scheme 3



the basis of analogy[11] the major isomer is speculated to be the *endo* isomer.

Intramolecular cyclization of the glycidyl carbamates **11b**, **11d**, or **16b** in pyridine solution, as described for the diester **11a**, furnished the corresponding oxazolidin-2-ones **12b**, **12d**, and **17b** in 75, 70, and 67% yields, respectively. The cyclization to the oxazolidin-2-one could not be demonstrated when pyridine was replaced by dioxane. In the ^{1}H-NMR spectra of these products the hydroxy proton appeared as a set of two triplets of equal intensity around 5.0 and 5.1 ppm. In the case of the ester **12a**, this hydroxy proton appeared as a single triplet. The presence of two triplets for the hydroxy group in the amides **12b**, **12d**, and **17b**, but not in the case of the ester **12a**, needs to be explained.

Depending upon whether the relative orientation of the ArCONH carbonyl groups is *cis–cis*, *cis–trans*, or *trans–trans*, with respect to the rigidly held hydroxymethyl group, the magnetic environments of the hydroxy group in these isomers could be different. It is most likely that in the case of the isophthalamides, as well as the dimethyl esters, all these geometric isomers are present at room temperature. However due to the expected and experimentally demonstrated[17] higher free energy of activation for free rotation around the Ar–(CO) bonds in the isophthalamides than in the case of the dimethyl esters, these isomers might be interconverting in the isophthalamides at a much slower rate, in the NMR time scale, than in the dimethyl esters. If this is true, then the splitting of the signal due to the hydroxy proton into two triplets in the case of the isophthalamides is not totally unexpected. In keeping with this trend, the ^{1}H-NMR as well as the ^{13}C-NMR spectra of the isophthalamides in general were more complex than those of the corresponding isophthalic esters, possibly arising from the potential for the former to exist in a larger number of atropisomeric forms.

Deacetylation of the tetraacetates **12b**, **12d**, and **17b** by treatment with sodium methoxide in methanol, followed by neutralization with Dowex-50-(H^+) resin and decolorization with charcoal, yielded the NICM candidates **12c**, **12e**, and **17c** as colorless glassy solids. These products were desalted and further purified by reverse-phase column chromatography over the Diaion CHP20 resin.[18] Crystallization from water or from aqueous 2-propanol afforded the three end products as white crystalline needles.

The NMR spectra of **12c**, **12e**, and **17c** in DMSO-d_6 were in full agreement with the structures assigned and with our expectation that they would exist as a mixture of several atropisomers, because of restriction to free rotation about the two Ar–(CO) bonds, the ArN–C(=O) bond, and the Ar–N bond, free rotation about which is known[11] to be restricted, when the N atom bears an alkyl group. Further complexity arose from *E–Z* isomerism due to restriction to free rotation about the two (CO)–NH bonds and the presence of the three asymmetric centers. The two N–H protons occurred as a set of six multiplets. As in the precursor acetates, the hydroxyl proton of the hydroxymethyl group occurred as a pair of two triplets apparently for reasons already explained in the case of the corresponding acetates. This hydroxyl proton was downshifted by 0.5 ppm from the rest of the hydroxy groups. This downshift could be attributed to the diamagnetic anisotropic effect of the phenyl ring. Molecular models reveal that this unique hydroxy group is held rigidly in a region above or below the π cloud of the aromatic ring. This effect of the triiodophenyl group is also felt by the C atom of the heterocycle-bound hydroxymethyl group, which was chemically shifted from the C atoms of the rest of the hydroxymethyl groups in compounds **12c**, **12e**, and **17c**.

The disposition of the signals due to the aromatic carbon atoms 2, 4, and 6, bearing the iodine atoms in the ^{13}C-NMR spectra of a few of the compounds described in this paper, is also worthy of comment. In the uncyclized derivatives, *viz.*, the glycidyl carbamates **11a**, **11b**, and **11d**, the C-2 carbon atom occurs at 88.5, 89.8, and 90.0 ppm, respectively. This assignment is based on the fact that these peaks in each of these compounds are almost half as intense as the corresponding signals at 100.7, 100.0, and 99.9 ppm, respectively, assignable to the magnetically equivalent C-4 and C-6 carbon atoms. In contradistinction, in all of the cyclized derivatives, such as compounds **12a**, **12b**, **12c**, **12d**, and **12e**, irrespective of substitution on the aromatic carbon atoms C-1 and C-3, three distinctly separate and nearly equal intense signals are observed. The C-2 carbon atom is seen around 90–92 ppm based on it being relatively insensitive to the heterocyclization of the 5-N atom. The C-4 and C-6 carbon atoms are seen around 97–98 and 101–102 ppm. In the dimethyl ester **12a** they occur as singlets and, in the isophthalamides **12c**, **12d** and **12e**, they are each split into two lines. We ascribe these phenomena to the fact that the carbon atoms C-4 and C-6 become magnetically nonequivalent on heterocyclization due to the combined effects of asymmetry imposed on the molecule as a result of restriction to free rotation around the Ar–N bond and the creation of an asymmetric C-4′ center consequent to heterocyclization. The further splitting of the peaks in the isophthalamides, and not in the dimethyl esters, is to be ascribed to the potential for the existence of a larger number of atropisomers. We have found that this pattern exhibited by the C-2, C- 4, and C-6 carbon atoms, before and after cyclization, is diagnostically useful in following the cyclization process in which the 5-N atom is alkylated and is part of an asymmetric heterocyclic lactam structure.

Conclusions

We have been able to demonstrate that sterically congested triiodobenzenoids directly attached to an α-branched 5-(hydroxymethyl)oxazolidin-2-one moiety through the nitrogen atom could be readily assembled by taking advantage of an intramolecular N-alkylation strategy on a suitably positioned oxirane function. α-Branched

(17) Laidlaw, G. M. Restricted Rotational Isomerism in Sterically Hindered Isophthalamides, Ph.D. Thesis, Rensselaer Polytechnic Institute, 1970; University Microfilms, Inc.: Ann Arbor, MI.
(18) Procured from Mitsubishi Corp, New York, NY.

5-*N*-alkyl-substituted triiodobenzenoids have so far not been accessible by intermolecular *N*-alkylation processes because of steric hindrance. The intramolecular *N*-cyclization proceeded with high regiospecificity and with no evidence of competitive *O*-cyclization under the base-catalyzed conditions employed. The intermediates and the final products exhibited complex but explicable NMR characteristics because of the presence of chiral centers and the potential for atropisomerism due to restricted rotation about single bonds in the molecules, coupled with the double bond character of the three amide bonds present in the molecule.

The new candidates were evaluated[2] for their potential to serve as X-ray diagnostic agents. As expected these were hydrolytically more stable in aqueous solution and the osmolality of 1 M aqueous solutions was also approximately 34% lower than that of iopamidol. Though the oxazolidin-2-one derivatives had many desirable physicochemical properties, their relatively poor water solubility (15 and 4% w/v for **12c** and **17c**, respectively, as determined by UV spectrophotometry) prevented further consideration for NICM applications for which the minimum water solubility required is approximately 80% w/v. An account of our efforts to construct other heterocyclic NICM using various intramolecular annulation strategies will be described in subsequent publications in this series.

Experimental Section

Phosgene was obtained from Fluka Chemical Corp. and (*S*)-glycidol was a gift from Dr. Collin Bayley, Norse Associates, Newbury Park, CA. Pyridine was purified by distillation over KOH. ^{1}H and ^{13}C resonances are at 270 and 75.5 MHz, respectively, and are given in δ values. Infrared spectra were obtained on KBr pellets. Melting points are uncorrected. All organic layers, obtained by extractive workup, were dried over anhydrous $MgSO_4$ and the solvents removed using a rotary evaporator at 40–50 °C. TLC analyses were carried out on precoated silica gel plates (2.5 × 10 cm) with a thickness of 250 μm. Normal-phase column chromatography was carried out using silica gel (70–230 mesh, 60 Å). HPLC elutions were performed with aqueous acetonitrile mixtures at a flow rate of 1.0 mL/min and pressure in the range 50–70 kg/cm^2. The extent of hydration of the new compounds reported was determined in every case either by the desorption or by the dissolution K-F titration method.

5-Amino-2,4,6-triiodo-1,3-benzenedicarboxylic Acid (6) An aqueous solution of potassium iododichloride (1.0 L, 2.1 M) (prepared fresh from ICl following a literature procedure[19]) was added dropwise over a period of 1 h to a suspension of the bis-acid **5** (115 g, 0.64 mol) in water (5 L), kept at 55–60 °C and the mixture was stirred for 18 h. The resulting suspension was cooled to 18 °C in an ice bath and filtered, and the fine brown solid was washed with water (4 × 250 mL), aqueous $NaHSO_3$ (0.5 M, 2 × 200 mL), and water (4 × 250 mL). The brown solid was dissolved in 0.66 N KOH solution (1.2 L) and filtered to remove insolubles. The pH of the solution was adjusted to 7 with 1 N HCl and the clear brown solution was decolorized at 50 °C with carbon (1.2 g). The precipitated solid, obtained upon acidification with concentrated HCl, was filtered and dried. Crystallization from a mixture of methanol (300 mL) and water (800 mL) furnished the triiodo bis-acid **6** as colorless crystals (260 g, yield 74%, purity 99.7%); HPLC (reverse phase C-8 column), retention time, 4.34 min in methanol/0.01 M H_3PO_4 containing 0.001 M $(Bu)_4NBr$ (3:7), detection at 254 nm; UV (MeOH) λ_{max} 233 nm (ϵ 28000); IR (KBr) 3392, 3381, 3350, 3286, 1714, 1656 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.56 (s, 2H), 13.76 (bs, 2H); ^{13}C-NMR ($CDCl_3$) δ 70.3, 78.1, 148.3 and 147.8, 169.7; MS *m/z* 560 (MH^+), 542, 516, 433, 416, 389. Anal. Found: C, 16.76; H, 0.95; I, 66.17; N, 2.21; H_2O (KF), 2.80. Calcd for $C_8H_4I_3NO_4 \cdot 0.89H_2O$: C, 16.71; H, 1.01; I, 66.22; N, 2.44.

5-Amino-2,4,6-triiodo-1,3-benzenedicarbonyl Dichloride (7). The bis-chloride **7** was prepared as described.[9] Thus, starting from the bis-acid **6** (130 g, 0.23 mol) and freshly purified thionyl chloride (1 L), crude bis-chloride **7** (133 g) was obtained. Crystallization from ethyl acetate–hexane afforded pure **7** (122 g, yield 92%, purity 99.4% by HPLC) as a yellow crystalline solid in two crops; mp 230–31 °C; TLC R_f 0.56 in ethyl acetate–hexane (1:3); HPLC (reverse phase C-8 column), retention time, 5.7 min in acetonitrile–water (8:2), detection at 254 nm; UV (MeOH) λ_{max} 233 nm (ϵ 24000); IR 3470, 3415, 3399, 1798, 1769, 1602 cm^{-1}; ^{13}C-NMR (acetone-d_6) δ 64.8, 76.9, 150.2, 150.7, 169.9; MS *m/z* 595 (MH^+), 560. Anal. Found: C, 16.23; H, 0.34; Cl, 11.92; I, 63.98; N, 2.19. Calcd for $C_8H_2Cl_2I_3NO_2$: C, 16.13; H, 0.34; Cl, 11.90; I, 63.91; N, 2.35.

Dimethyl 5-Amino-2,4,6-triiodo-1,3-benzenedicarboxylate (8a). A solution of **6** (5.59 g, 10 mmol) in methanol (10 mL) was treated at 0 °C with an ethereal solution of diazomethane prepared from Diazald (10 g, 23 mmol) and aqueous KOH (10 g in 16 mL of water). The reaction mixture was kept at 0 °C for 2 h and allowed to warm to ambient temperature overnight. The solvents were distilled off, and the residue was crystallized from a mixture of methanol and ether to obtain **8a** as colorless plates (5.43 g, yield 98%): mp 163–64 °C; TLC R_f 0.45 in 1:4 ethyl acetate/hexane; HPLC (reverse-phase C-8 column), retention time, 9.4 min in 7:3 acetonitrile/water, 0.5 mL/min; UV ((MeOH) λ_{max} 233 nm (ϵ 27000); IR (KBr) 1730, 1675, 1671 cm^{-1}; ^{1}H-NMR (DMSO) δ 3.90 (s, 6H), 5.75 (bs, 2H); ^{13}C-NMR (DMSO) δ 53.0, 71.1, 79.5, 148.2, 146.6, 168.4; MS *m/z* 587 (M^+), 556, 461. Anal. Found: C, 20.73; H, 1.31; I, 64.83; N, 2.49. Calcd for $C_{10}H_8I_3NO_4$: C, 20.46; H, 1.37; I, 64.87; N, 2.39.

5-Amino-*N,N'*-bis[2,3-bis(acetyloxy)propyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (8b). To a solution of the bis-chloride **7** (34 g, 0.057 mol) in anhydrous DMA (200 mL) was added 1-amino-2,3-propanediol (22 g, 0.24 mol) in DMA (50 mL) over a period of 30 min and the solution was stirred at ambient temperature for 16 h. The solvent was removed and the residue, containing the *bis*-amide **8a**, was treated with acetic anhydride (100 g, 1 mol) in pyridine (200 mL) over 30 min such that the temperature did not exceed 50 °C. The reaction mixture was stirred at room temperature for 6 h. Water (20 mL) was added, and the solvents were removed. Residual pyridine was removed by codistillation with toluene (100 mL). The product was redissolved in ethyl acetate (300 mL) and then washed with water (2 × 100 mL), 1 N HCl (2 × 100 mL), followed by water (2 × 100 mL), saturated aqueous $NaHCO_3$ (2 × 100 mL), water (2 × 100 mL), and brine (100 mL). The organic layer was dried and the solvent removed to obtain the crude product **8b** (71 g), which was purified by column chromatography over silica gel (500 g) using a mixture of ethyl acetate and hexane (3:1) to obtain pure **8b** as an off-white glassy solid (47 g, yield 94%); TLC R_f 0.50 in $CHCl_3$–methanol (9:1); HPLC (reverse-phase C-8 column), retention time, 2.9 min in acetonitrile–water (7:3); UV (MeOH) λ_{max} 231 nm (ϵ 29800); IR(KBr) 3445, 3344, 1733, 1661 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.02 (s, 12H), 3.2–3.6 (m, 4H,), 4.1–4.4 (m, 4H), 5.05–5.2 (m, 2H), 5.5 (s, 2H), 8.40 and 8.67 (2q, 2H); ^{13}C NMR ($CDCl_3$) 20.7, 21.2, 39.8, 63.3, 70.2, 72.8, 79.3, 147.2, 148.5, 170.3, 170.7; MS *m/z* 874 (MH^+), 832, 814, 669, 573. Anal. Found: C, 30.58; H, 2.93; I, 43.77; N, 4.75. Calcd for $C_{22}H_{26}I_3N_3O_{10}$: C, 30.26; H, 3.00; I, 43.60; N, 4.81.

***N,N'*-Bis[2-(acetyloxy)-1-[(acetyloxy)methyl]ethyl]-5-amino-2,4,6-triiodo-1,3-benzenedicarboxamide (8d).** The procedure was essentially the same as the one used for the preparation of **8b**. Thus, starting from **7** (50 g, 84 mmol) and 2-amino-1,3-propanediol [liberated from the corresponding hydrochloride (45.02 g, 0.35 mol) in anhydrous DMA (440 mL), NaH (10.2 g, 0.42 mmol) over 20 min], followed by purification by crystallization from ethyl acetate, **8d** was obtained as a white crystalline solid (63.6 g, yield 87%): mp 195–7 °C; HPLC (reverse-phase C8 column), retention time, 2.9 min in acetonitrile–water (7:3); UV (CH_3CN) λ_{max} 231 nm (ϵ 29300); IR (KBr) 3700, 1733, 1657 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.02 (s, 12H), 4.12 (m, 8H), 4.32 (m, 2H), 5.5 (s, 2H), 8.7 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 20.7, 46.9, 62.0, 73.4, 79.7, 147.5, 148.5,169.5, 170.2; MS *m/z* 874 (MH^+),

(19) Larsen, A. A.; Moore, C.; Sprague, G.; Cloke, B.; Moss, J.; Hoppe, H. O. *J. Am. Chem. Soc.* **1956**, *78*, 3210.

832, 814, 748, 699, 573. Anal. Found: C, 30.33; H, 2.98; I, 43.96; N, 4.57. Calcd for $C_{22}H_{26}I_3N_3O_{10}$: C, 30.26; H, 3.00; I, 43.60; N, 4.81.

Dimethyl 2,4,6-Triiodo-5-[[(oxiranylmethoxy)carbonyl]amino]-1,3-benzenedicarboxylate (11a). To a solution of **8a** (3.54 g, 6 mmol) in dioxane (30 mL) was added a 2 M toluene solution of phosgene (33 mL, 66 mmol). [***CAUTION***: Phosgene is highly toxic with a dangerous delayed effect and its use is recommended only in a well-ventilated hood. The concentration of phosgene in the hood should be monitored as reported[20]]. The flask was stoppered with a rubber septum and wired tightly and the reaction mixture was stirred at 60 °C for 15 h. The solvents were removed under vacuum by slowly raising the temperature to 85–90 °C with exclusion of moisture. Excess phosgene and gaseous HCl were decomposed by passing the effluents through a 20% solution of aqueous NaOH. Dioxane (50 mL) was added to the residue and was slowly distilled off, this process being repeated twice. The residual solid containing the product **9a** was redissolved in dioxane (30 mL), and glycidol (**10**) (0.67 g, 9 mmol) and phenylmercuric acetate (100 mg) were added with stirring at room temperature. The reaction mixture was stirred for 4 h. The solvent was removed *in vacuo*, the residue dissolved in ethyl acetate (100 mL), and the solution extracted with water (2 × 25 mL), and dried. Solvent removal afforded a white solid, which was purified by crystallization from a mixture of ethyl acetate and hexane affording **11a**, as off-white plates (2.75 g, yield 66%). The residue obtained from the mother liquor was purified by silica gel (25 g) column chromatography using ethyl acetate–hexane (1:1) to obtain an additional 0.6 g of the pure product, bringing the total yield to 81%: mp 178–80 °C; TLC R_f 0.50 in ethyl acetate–hexane (1:1), R_f 0.41 in benzene–ethyl acetate (8:2); UV (MeOH) λ_{max} 241 nm (ϵ 32000); IR (KBr) 3443, 3420, 3391, 1734, 1729, cm^{-1}; ^{1}H-NMR (DMSO) δ 2.51–2.53 (25%) and 2.69–2.72 (75%) (d of d, J_{gem} 5.0 Hz, J_{vic} 2.7 Hz, 1H), 2.69–2.72 (25%) and 2.79–2.82 (75%) (t, J_{gem} 4.7 Hz, J_{vic} 4.2 Hz, 1H), 3.10 (25%) and 3.20–3.28 (75%) (m, 1H); 3.80–3.97 (m, 1H), 3.90 (s, 6H); 4.29–4.35 (25%) and 4.42–4.48 (75%) (d of d, J_{gem} 12.6 Hz, J_{vic} 2.9 Hz, 1H), 9.40 (25%) and 9.74 (75%) (s, 1H); ^{13}C-NMR (DMSO) δ 43.7, 49.1, 49.3, 53.3, 65.4, 65.6, 88.5, 100.7, 142.8, 147.6; 152.4, 153.1, 167.8, 167.9; MS *m/z* 688 (MH$^+$), 655, 614. Anal. Found: C, 24.64; H, 1.73; I, 55.36; N, 1.96. Calcd for $C_{14}H_{12}I_3NO_7$: C, 24.48, H, 1.76; I, 55.42; N, 2.04.

[3,5-Bis[[[2,3-bis(acetyloxy)propyl]amino]carbonyl]-2,4,6-triiodophenyl]carbamic Acid, Oxiranylmethyl Ester (11b). The procedure used for **11a**, was followed starting from **8b** (30.0 g, 34 mmol), phosgene (2 M solution, 170 mL, 340 mmol), and glycidol (5.4 g, 71 mmol). Purification of the crude product by crystallization from ethyl acetate and hexane afforded **11b** as a white crystalline powder (25.6 g, yield 76.5%); mp 142–145 °C; TLC R_f 0.43 in $CHCl_3$–methanol (9:1); UV (MeOH) λ_{max} 241 nm (ϵ 28800); IR (KBr) 3445, 3435, 1735, 1659 cm^{-1}; ^{1}H-NMR (DMSO) δ 2.02 (s, 12 H), 2.57–2.60 (20%) and 2.68–2.74 (80%) (d of d, J_{gem} = 4.9 Hz, J_{vic} = 2.8 Hz, 1H,), 2.71–2.74 (20%) and 2.80–2.84 (80%) (t, J_{gem} = J_{vic} = 4.95 Hz, 1H), 3.08–3.20 (20%) and 3.20–3.26 (80%) (m, 1H), 3.3–3.92 (m, 4H), 3.75–3.84 (20%) and 3.85–3.92 (80%) (d of d, J_{gem} = 12.63 Hz, J_{vic} = 6.69 Hz, 1H), 4.10–4.45 (m, 5 H), 5.07–5.11 (m, 2H), 8.45–8.54 (20%) and 8.80–9.05 (80%) (4t, 2H); 9.45 (20%) and 9.62 (80%) (2s, 1H); ^{13}C-NMR (DMSO) δ 20.5, 20.9, 39.2, 43.7, 49.4, 62.9, 65.3, 69.5, 90.0, 99.7, 142.2, 149.9, 153.1, 169.6, 169.8, 170.1; MS *m/z* 974 (MH$^+$), 914, 872, 799, 673, 440. Anal. Found: C, 32.25; H, 3.08; I, 39.06; N, 4.17. Calcd for $C_{26}H_{30}I_3N_3O_{13}$: C, 32.09; H, 3.11; I, 39.12; N, 4.32.

[3,5-Bis[[[2-(acetyloxy)-1-[(acetyloxy)methyl]ethyl]amino]carbonyl]-2,4,6-triiodophenyl]carbamic Acid, Oxiranylmethyl Ester (11d). The procedure used for **11a** was followed starting from **8d** (14.4 g, 16.5 mmol), phosgene (2 M solution, 124 mL, 248 mmol), and glycidol (3.1 g, 41.3 mmol). Purification of the crude product by crystallization from methanol afforded **11d** as an off-white solid (12 g, yield 75%): mp 228–30 °C; TLC R_f 0.60 in $CHCl_3$–methanol (9:1), R_f 0.70 in ethyl acetate–hexane (8:2); UV (CH_3CN) λ_{max} 243 nm (ϵ 29300); IR (KBr) 3439, 1733, 1658 cm^{-1}; ^{1}H-NMR (DMSO) δ 2.05 (s, 12H), 2.56–2.64 (10%) and 2.71–2.74 (90%) (d of d, J_{gem} = 4.7 Hz, J_{vic} = 2.3 Hz, 1H), 2.71–2.74 (10%) 2.80–2.84 (90%) (t, J_{gem} = J_{vic} = 5.3 Hz, 1H), 3.08–3.20 (10%) and 3.20–3.26 (90%) (m, 1H), 3.75-3.84 (10%) and 3.84–3.96 (90%) (d of d, J_{gem} = 11.1 Hz, J_{vic} = 6.1 Hz, 1H), 4.05 and 4.25 (bd, 8H), 4.26–4.50 (m, 3H), 8.55–8.60 (10%) and 8.80–9.02 (90%) [4d, J = 8.2 Hz, 2H), 9.37 (10%) and 9.67 (90%) (2s, 1H); ^{13}C-NMR (DMSO) δ 20.7, 43.7, 46.9, 49.4, 62.0, 65.3, 90.0, 99.9, 142.2, 149.6, 153.2, 169.0, 170.2; MS *m/z* 974 (MH$^+$), 914, 848, 799, 722, 673. Anal. Found: C, 31.62; H, 3.04; I, 38.43; N, 4.30; H_2O (KF), 2.22. Calcd for $C_{26}H_{30}I_3N_3O_{13}$·1.23H_2O: C, 31.37; H, 3.29; I, 38.25; N, 4.22.

[3,5-Bis-[[[2,3-bis(acetyloxy)propyl]amino]carbonyl]-2,4,6- triiodophenyl]carbamic Acid, (*S*)-Oxiranylmethyl Ester (16b). The procedure used for **11a**, was followed starting from **8b** (8.10 g, 0.93 mmol), phosgene (2 M solution, 55 mL, 110 mmol), and (*S*)-glycidol (**10**) (1.4 mL, 21 mmol, 84.6% ee). Purification of the crude product by silica column chromatography using hexane/ethyl acetate afforded **16b** as a colorless glassy solid (5 g, yield 60%): mp 115–118 °C; TLC R_f 0.35 in ethyl acetate/hexane (9:1); UV, IR, ^{1}H-NMR, ^{13}C-NMR, and MS data were identical with those reported for the compound **11b**; α $^{25}_D$ +3.68° (*c* 2.0, MeOH). Anal. Found: C, 32.32; H, 3.02; I, 39.37; N, 4.40. Calcd for $C_{26}H_{30}I_3N_3O_{13}$: C, 32.09; H, 3.11; I, 39.12; N, 4.32.

Dimethyl 5-[4-(Hydroxymethyl)-2-oxo-3-oxazolidinyl]-2,4,6- triiodo-1,3-benzenedicarboxylate (12a). A solution of the oxiranylmethyl ester **11a** (2.5 g, 3.64 mmol) in anhydrous pyridine (50 mL) was heated at 75 °C for 2 h. Pyridine was removed *in vacuo* and the residue coevaporated twice with toluene (100 mL) to remove residual pyridine. The residue was dissolved in ethyl acetate (100 mL) and an insoluble brown-colored fluffy residue (40 mg) filtered off. The filtrate was extracted with water (2 × 50 mL), 1 N HCl (2 × 50 mL), water (2 × 50 mL), and brine (50 mL). The organic layer was dried and solvent removal afforded the crude product as an off-white solid (2.50 g). Silica gel (50 g) column chromatography using ethyl acetate–hexane (8:2) yielded **12a** as a white glassy solid (1.85 g, yield 74%); TLC R_f 0.32 in ethyl acetate–hexane (1:1), R_f 0.32 in benzene–ethyl acetate (6:4); λ_{max} 244 nm (ϵ 30200); IR (KBr) 3450, 3446 ,1741 cm^{-1}; ^{1}H-NMR (DMSO) δ 3.60–3.73 (m, 2H), 3.91 and 3.92 (2s, 6H), 4.28 (dd, J_{gem} 8.8 Hz, J_{vic} 6.5 Hz, 1H), 4.46–4.56 (m, 1H), 4.67 (t, J_{gem} = J_{vic} = 8.8 Hz, 1H), 4.94 (t, J_{vic} 4.7 Hz, 1H); ^{13}C-NMR (DMSO) δ 54.2, 59.4, 62.8, 66.8, 90.4, 98.4,103.4, 143.3, 148.9, 155.3, 168.6; MS *m/z* 688 (MH$^+$), 656, 560. Anal. Found: C, 24.95; H, 1.81; I, 55.54; N, 2.01. Calcd for $C_{14}H_{12}I_3NO_7$: C, 24.48, H, 1.76; I, 55.42; N, 2.04.

***N,N'*-Bis[2,3-bis(acetyloxy)propyl]-5-(4-hydroxymethyl)-2-oxo-3-oxazolidinyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (12b).** The procedure used for **12a** was followed starting from **11b** (30 g, 0.3 mol) and pyridine (300 mL). Purification of the crude product by crystallization from methanol furnished **12b** as colorless needles (22.6 g, yield 75%): mp 278–80 °C; TLC R_f 0.29 in $CHCl_3$–methanol (9:1); UV (MeOH) λ_{max} 240 (ϵ 29300); IR (KBr) 3432, 1739, 1662 cm^{-1}; ^{1}H-NMR (DMSO) δ 2.03 (s, 12H), 3.48–3.60 (m, 5H), 3.65–3.85 (m, 1H), 4.10–4.55 (m, 6H), 4.61–4.75 (m, 1H), 4.95–5.20 (m, 3H); 8.62–9.04 (4t, 2H); ^{13}C-NMR ($CDCl_3$) δ 20.8 and 21.2, 39.9, 58.5, 58.9, 62.8, 63.4, 67.0, 67.7, 69.9, 90.3, 97.1, 101.2, 101.9, 141.6, 142.1, 150.3, 150.5, 152.7, 153.1, 169.6, 169.8, 170.2; MS *m/z* 974 (MH$^+$), 914, 873, 788, 671, 545. Anal. Found: C, 32.07; H, 3.19; I, 39.07; N, 4.07. Calcd for $C_{26}H_{30}I_3N_3O_{13}$: C, 32.08; H, 3.11; I, 39.12; N, 4.32.

***N,N'*-Bis[2-(acetyloxy)-1-[(acetyloxy)methyl]ethyl]-5-[4-(hydroxymethyl)-2-oxo-3-oxazolidinyl]-1,3-benzenedicarboxamide (12d).** The procedure used for **12a** was followed starting from **11d** (12.1 g, 12.4 mmol) and pyridine (120 mL). Purification of the crude product by crystallization from methanol afforded **12d** as colorless needles (8.5g, yield 70%): mp 235–40 °C; TLC R_f 0.6 in $CHCl_3$–methanol (9:1); HPLC (reverse-phase C-8 silica column), retention time, 2.4 min in acetonitrile–water (7:3), (98.7% pure); UV (CH_3CN) λ_{max} 243 nm (ϵ 31000); IR (KBr) 3440, 3354, 1740, 1660 cm^{-1}; ^{1}H-NMR (DMSO) δ 2.03 and 2.04 (2s, 12H), 3.45–3.65 (m, 1H), 3.70–3.85 (m, 1H), 4.10–4.25 (m, 8H), 4.25–4.48 (m, 4H), 4.62-4.77 (m, 1H), 5.02 and 5.10 (2t, 1H), 8.46–9.04 (m, 2H); ^{13}C-NMR (DMSO) δ 20.7, 47.0, 58.4 and 58.6, 62.0, 67.3, 67.5, 92.2, 97.7, 97.8, 102.2, 102.5, 141.2, 141.4, 150.3, 150.4, 154.1, 154.2, 168.9, 170.2; MS *m/z* 974 (MH$^+$), 913, 871, 847, 670.

(20) Budavi, S., Ed., *The Merck Index*, (11th ed.; Merck & Co. Inc., 1989, p 1165.

Anal. Found: C, 32.18; H, 3.22; I, 38.73; N, 4.29. Calcd for $C_{26}H_{30}I_3N_3O_{13}$: C, 32.08; H, 3.11; I, 39.12; N, 4.32.

***N,N'*-Bis[2,3-bis(acetyloxy)propyl]-5-[4(R)-(hydroxymethyl)-2-oxo-3-oxazolidinyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (17b).** The procedure used for **12a** was followed starting from **14b** (2.45 g, 0.25 mmol) and pyridine (25 mL). Purification of the crude product by silica gel column chromatography using ethyl acetate as the eluent provided **17b** as a colorless glassy solid (1.68 g, yield 68.6%): TLC R_f 0.43 in ethyl acetate–methanol (97:3); The UV, IR, ^{1}H-NMR, ^{13}C-NMR, and MS data were identical with those found for compound **12b**. α^{25}_D +9.3° (*c* 1.0, MeOH). Anal. Found: C, 32.17; H, 3.13; I, 39.28; N, 4.18. Calcd for $C_{26}H_{30}I_3N_3O_{13}$: C, 32.08; H, 3.11; I, 39.12; N, 4.32.

N,N'-Bis(2,3-dihydroxypropyl)-5-[4-(hydroxymethyl)-2-oxo-3-oxazolidinyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (12c). To a solution of 12b (18 g, 0.0184 mol) in anhydrous methanol (180 mL) was added a solution of sodium methoxide (1.08 g, 0.02 mol) in methanol (20 mL) and the mixture stirred for 1 h. Dowex-50(H^+) resin was added to this solution until the pH was brought down to ~7. The resin was filtered off and the residue, obtained after the removal of methanol, was dissolved in water (150 mL). The solution was decolorized by boiling for 15 min with Darco (200 mg), and solvent removal afforded a colorless glass (14.1g). This material was purified by reverse-phase column chromatography, using the nonionic Diaion-CHP-20 resin.[18] The loaded column was washed with water to remove inorganic salts and then eluted with 2% aqueous ethanol. The fractions containing the product were combined and the solvents removed to obtain the product as a white powder. Crystallization from water afforded pure 12c as fine white needles (10.85 g, yield 73%); mp 315–20 °C (dec); UV (H_2O) λ_{max} 254 nm (ϵ 30000); IR (KBr) 3475, 3412, 1737,1647, 1636 cm^1; ^{1}H-NMR (DMSO) δ 3.02–3.55 (m, 9H), 3.58–3.80 (bs, 3H), 4.30–4.45 (m, 4H), 4.60–4.78 (m, 3H), 4.99 and 5.07 (2t, 1H), 7.46–8.38 (m, 2H); ^{13}C-NMR (DMSO) δ 42.8 and 42.9, 58.7, 58.9, 62.3, 64.2, 67.7, 70.2, 70.4, 92.8, 97.7, 98.1, 102.3, 102.7, 141.2 and 141.4, 151.1, 154.4 and 154.6, 169.7; MS *m/z* 806 (MH^+), 680, 587, 497, 399. Anal. Found: C, 25.95; H, 2.84; I, 45.33; N, 4.89; H_2O (KF), 3.51. Calcd for $C_{18}H_{22}I_3N_3O_9 \cdot 1.63H_2O$: C, 25.91; H, 3.05; I, 45.63; N, 5.04.

***N,N'*-Bis[2-hydroxy-1-(hydroxymethyl)ethyl]-2,4,6-triiodo-5-[4-(hydroxymethyl)-2-oxo-3-oxazolidinyl]-1,3-benzenedicarboxamide (12e).** The procedure used for **12c** was followed starting from **12d** (4.2 g, 4.3 mmol) and sodium methoxide (88 mg, 1.6 mmol). Purification of the crude product by reverse-phase Diaion-CHP20 resin[18] column chromatography using 8% ethanol as the eluent, followed by crystallization from isopropanol, furnished **12e** as colorless needles (3.2 g, yield 92%); UV (H_2O) λ_{max} 245 nm (ϵ 28900); IR (KBr) 3413, 3281, 1737, 1641 cm^{-1}; ^{1}H-NMR (DMSO) δ 3.42–3.78 (m, 10H), 3.78–3.95 (bs, 2H), 4.30–4.52 (m, 2H); 4.40–4.60 (m, 4H), 4.60–4.74 (m, 1H), 4.99 and 5.07 (2t, 1H), 7.46–8.38 (m, 2H); ^{13}C-NMR (DMSO) δ 52.9, 53.2, 58.3, 58.6, 59.1, 59.2, 59.3, 62.0, 62.1, 67.4, 92.5, 97.3, 101.8, 102.2, 102.3, 140.9, 141.1, 150.7, 154.2, 154.3, 168.8, 168.8, 168.9; MS *m/z* 806 (MH^+), 678, 578, 433. Anal. Found: C, 26.07; H, 2.82; I, 46.15; N, 4.94; H_2O (KF), 3.09. Calcd for $C_{18}H_{22}I_3N_3O_9 \cdot 1.42H_2O$: C, 26.02; H, 3.01; I, 45.83; N, 5.06.

***N,N'*-Bis(2,3-dihydroxypropyl)-5-[4(R)-(hydroxymethyl)-2-oxo-3-oxazolidinyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (17c).** The procedure used for **12c**, was followed starting from **16b** (410 mg, 0.51 mmol) and sodium methoxide (22 mg, 0.4 mmol). Purification of the crude product by reverse-phase Diaion-CHP20 resin[18] column chromatography using 2% ethanol as the eluent, followed by crystallization from water, provided **17c** as colorless needles (320 mg, yield, 84%): TLC R_f 0.3 in methanol/$CHCl_3$ (3:7); The UV, IR, ^{1}H-NMR, ^{13}C-NMR, and MS data were identical with those found for the compound **12c**; α^{25}_D + 9.9° (*c* 1.0, MeOH). Anal. Found: C, 26.02; H, 2.89; I, 45.92; N, 4.90, H_2O (KF), 3.50. Calcd for $C_{18}H_{22}I_3N_3O_9 \cdot 1.6H_2O$: C, 25.91; H, 3.05; I, 45.63; N, 5.04.

Acknowledgment. We wish to acknowledge Dr. M. Tweedle and Dr. W. C. Eckelman for helpful discussions and encouragement throughout this work, Drs. A. C. Chang, K. Kumar, and M. Garrison, Mr. Z. Ugwuneri, and Mrs. M. Fernandez for physical measurements, and Mr. P. Wedeking for biological studies. We also thank the BMSPRI Analytical Division for spectral data and elemental analysis determinations.