Heterocyclic Nonionic X-ray Contrast Agents. 4. The Synthesis of Dihydro-2(3*H*)-furanylidenamino, 5-Oxo-1-pyrrolidinyl, and 5-Oxo-4-morpholinyl Derivatives by an Intramolecular Iodocyclization Approach†

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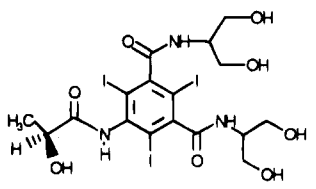
Intramolecular iodocyclization of ω-alkenylanilides **6** and [ω-(alkenyloxy)alkyl]anilides **7** resulted in the formation of dihydro-2(3*H*)-furanylidenamines **8** and 1,4-dioxan-2-ylideneamines **9**, respectively, by an amide-oxygen participative nucleophilic attack on the expected iodonium intermediate. The latter heterocyclic ring system is new. If a strong base is present, the mode of ring closure was mainly diverted to an amide-nitrogen participative nucleophilic attack, leading to (iodomethyl)-pyrrolidinones **10** and (iodomethyl)morpholinones **11**, from **6** and **7**, respectively. Unique interconvertible *syn–anti* isomerism in the imino-ether **8a** was demonstrated by variable temperature NMR studies. The major component in this mixture was the **8a-*anti***-isomer. Acetolysis of the iodocyclized products, followed by deacetylation, provided the heterocyclically substituted polyhydroxytriiodoisophthalamides **16–18**. Hydrolytic studies on the imidate **16d** revealed an interesting pH dependence. As expected the amine **3d** and the amide **22** resulted in pH values of 2 and 6. At pH 12, however, the Chapman rearrangement product **17d** was the major product. The compounds obtained in this investigation are of interest as X-ray contrast agents.

Introduction

We have earlier[1] presented the rationale for designing X-ray contrast agents based on the attachment of azaheterocyclic moieties at the 5 position of 2,4,6-triiodo-1,3-benzenedicarboxamides via the nitrogen atom of the heterocycle. The main aim was to develop new and improved nonionic iodinated contrast media[2] (NICM) having greater stability and lower osmolality than currently employed radiographic agents, such as Iopamidol[3] (**1**) or Iohexol[4] (**2**).



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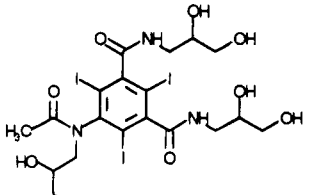

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In part 3[1] the syntheses of oxazolidin-2-one-based 2,4,6-triiodo-1,3-benzenedicarboxamide derivatives were presented. These compounds had lower osmolality and greater stability, but lacked the required high water solubility of >80% w/v. In this paper we discuss the synthesis and evaluation of 2-(hydroxymethyl)pyrrolidin-5-one derivatives **17** and 3-(hydroxymethyl)morpholin-5-one derivatives **18** using iodocyclization methodology.[5] The choice of these two lactams was based on the ubiquitous presence of the carboxamide linkage as a hydrophilic and detoxifying element in the design of NICM.[2] Also described herein are the syntheses of dihydro-5-(hydroxymethyl)-2(3*H*)-furanylideneamino congeners **16** that resulted during our initial attempts to prepare the pyrrolidine derivatives under nonbasic conditions.

Results and Discussion

The required ω-alkenyl anilides **6** and **7** were prepared (Scheme 1) in high yield by acylation of the previously described[1] amino compounds **3a**, **3b**, or **3c** with 4-pentenoyl chloride[6a] (**4**) or (allyloxy)acetyl chloride[6b,c] (**5**), respectively, in dimethylacetamide (DMA) at room temperature. We initially carried out a model study on the dimethyl esters **6a** and **7a**, which offered simpler systems allowing us to explore the course of the heterocyclic ring forming reactions.

Synthesis of 5-(Iodomethyl)-2-furanylideneamines 8 and 2-(Iodomethyl)pyrrolidin-5-ones 10. The heterocyclic ring systems **8** and **9** were constructed in one step from the ω-alkenyl anilides **6** or **7**, respectively, utilizing the intramolecular iodocyclization methodology[5] depicted in Scheme 1. Treatment of **6a** with *N*-iodosuccinimide (NIS) (2.0 equiv) in $CHCl_3$ at 50 °C for 1 h afforded exclusively the imino ether **8a** in 79% isolated yield. When this reaction was carried out with NIS (2.2 equiv) in dioxane–methanol containing aqueous NaOH (5 equiv), the more polar lactam **10a** resulted as

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(1) (a) Part 1: 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. (b) Part 2: *Ibid.* Manuscript in preparation. (c) Part 3: Pillai, K. M.R.; Diamantidis, G.; Duncan, L.; Ranganathan, R. S. *J. Org. Chem.* **1994**, *59*, 1344.

(2) (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; Sec. 76, Vol. 1, pp 23–131. (b) Hoey, G. B.; Smith, K. R. *Chemistry of X-Ray Contrast Media.* In *Radiocontrast Agents*; Sovak, M., Ed.; Springer-Verlag: Basel, 1984; pp 23–125.

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

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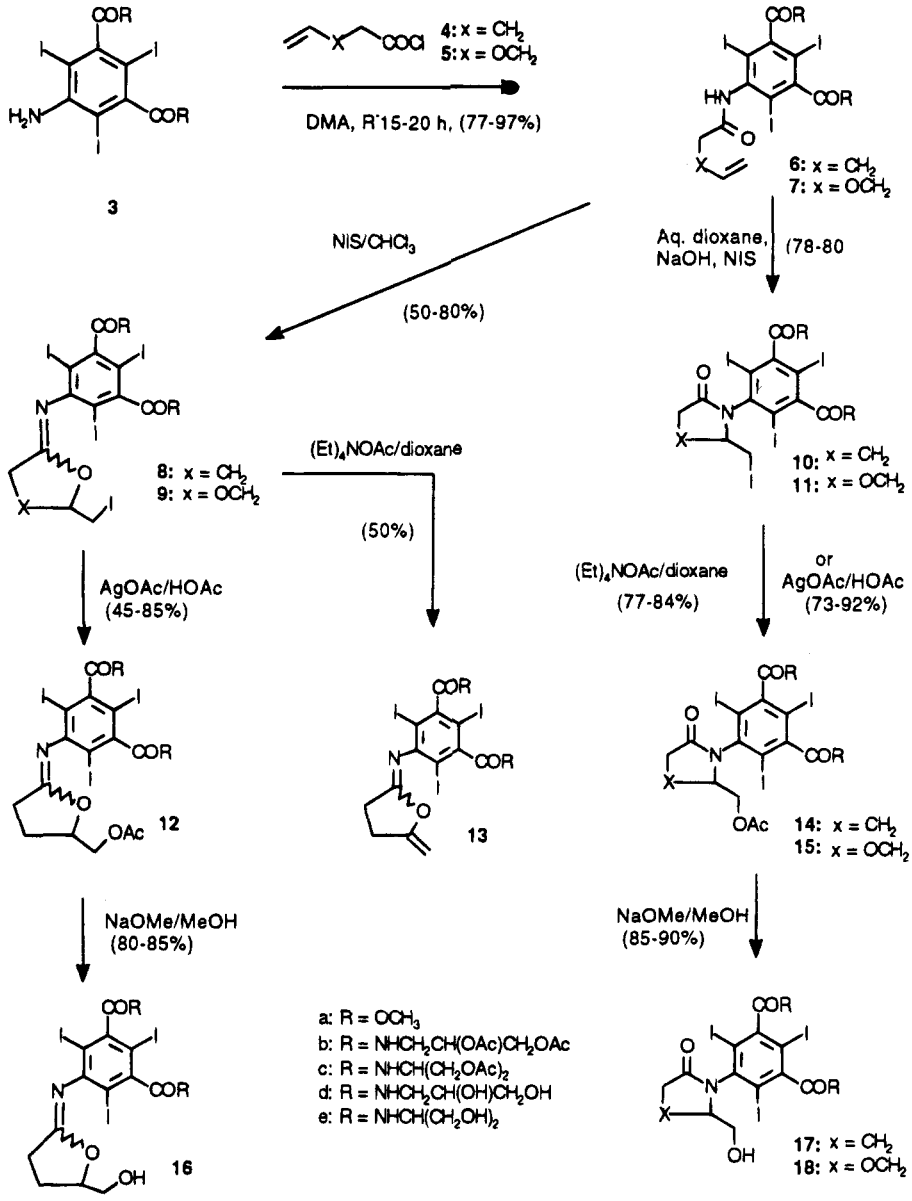
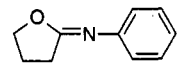
Scheme 1



the major product (96%), along with **8a** (4%). The change in the course of the iodocyclization from one of exclusive oxygen participation to one of predominant nitrogen participation by the simple expediency of the addition of a strong base is noteworthy and striking.

The spectral data of the iodocyclization products, particularly the furanylideneamine **8a**, deserve comment. Interestingly, the IR spectrum of **8a** showed a strong absorption in the carbonyl region at 1703 cm^{-1} for the O—C=N system, which is higher than the value (1687 cm^{-1}) reported[7] for the analogous cyclic imidate **19**. This is indicative[8] of a lower degree of conjugation between the π systems of the C=N and phenyl groups in **8a** than in **19**, due to steric overcrowding caused by the triiodination of the phenyl ring and bridging at the 5′ position of the heterocycle. The ^{13}C-NMR spectrum of **8a** showed signals at 82.4 ppm for the OCH carbon[9] and at 162.5 ppm for the imidate carbon (OC=N), whereas the lactam **10a** exhibited signals at 61.2 ppm for the NCH carbon[5] and at 162.2 ppm for the lactam carbon (NC=O).



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The signal for the iodomethyl carbon[10] in **8a** and **10a** appeared at 6.5 and 6.7 ppm, respectively, and this clearly ruled out the corresponding six-membered heterocyclic structures that could result by attack on the terminal carbon of the iodonium intermediate. The observed nonformation of six-membered ring systems under iodocyclization conditions is in full conformity with the reported preference for the 5-*exo*-tet process over the 6-*exo*-tet process.[11]

(7) Saito, H.; Nukada, K. *Tetrahedron*, **1966**, *22*, 3313. See also Deyrup, J. A.; Gingrich, H. L. *J. Org. Chem.* **1977**, 42, 1015.
(8) Bellamy, L. J. *The Infrared Spectra of Complex Molecules*, 2nd ed.; Chapman and Hall: New York, 1980; Vol. 2, p 54.
(9) Barbaro, G; Battaglia, A.; Giorgianni, P. *J. Org. Chem.* **1988**, *53*, 5501–5506. Evans, R. D.; Magee, J. W.; Schauble, J. H. *Synthesis* **1988**, 862.
(10) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. In *Spectrometric Identification of Organic Compounds*; 5th ed.; John Wiley & Sons, Inc.: New York, 1991; p 236.
(11) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

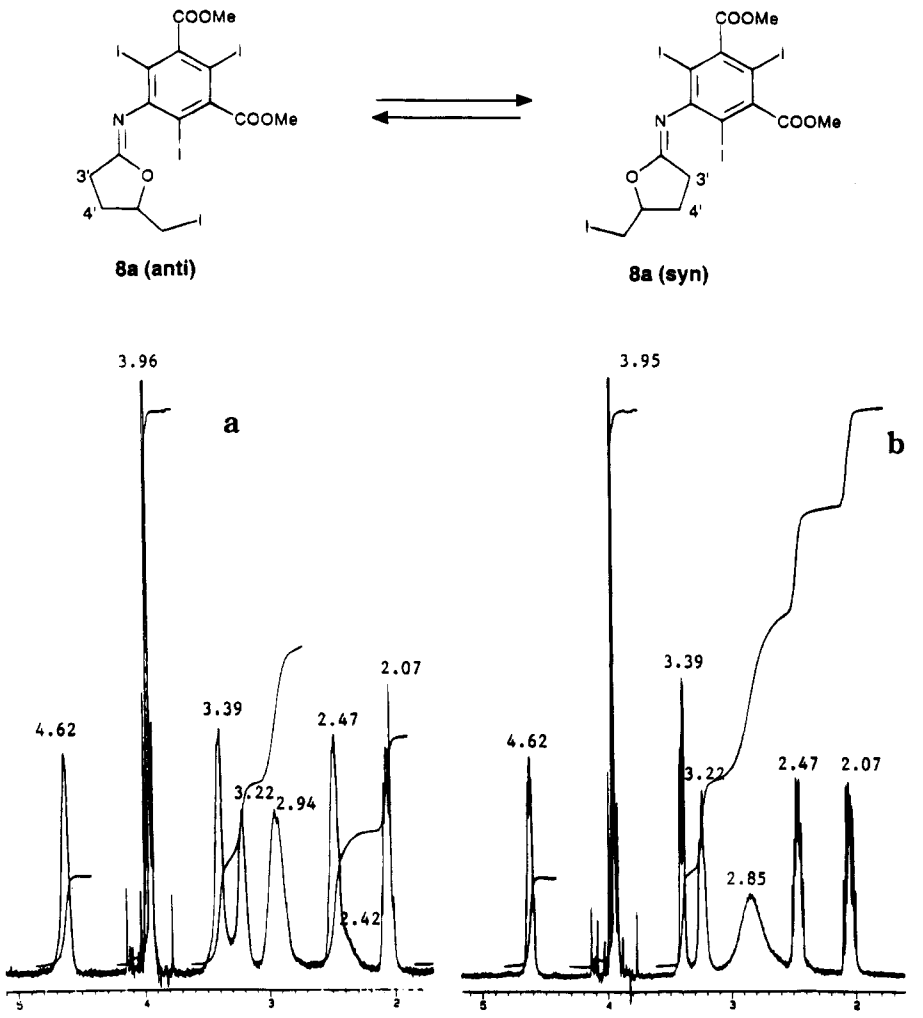


Figure 1. 400 MHz ^{1}H NMR spectrum of **8a** at (a) 37 °C; (b) 55 °C.

The proton NMR (270 MHz) spectrum of the lactam **10a** showed sharp well resolved peaks characteristics of the expected lactam structure, while the furanylideneamino **8a** exhibited poorly resolved broad peaks with anomalous integration values. To improve resolution the ^{1}H-NMR spectrum of **8a** was recorded at 400 MHz at 37 °C. However, the peaks in **8a** continued to remain broad and the peaks centered at 2.07, 2.47, and 2.94 ppm integrated for 1.0, 1.5, and 1.5 protons, respectively, rendering data interpretation difficult. A likely explanation could be that **8a** exists at room temperature as a slow equilibrating mixture of the corresponding *syn* and *anti* forms. Careful analysis of the 400 MHz NMR data indeed provided support for this view (Figure 1).

Two broad peaks at 2.42 and 2.94 ppm, separated by 0.52 ppm, were observed for the C-3′-methylene protons. In related molecules, such as the imidate **19**, it has been noticed[7] that the α-methylene protons are split into two resonances. This has been attributed to the diamagnetic anisotropy of the phenylimino group, which results in the shielding of the α-methylene protons in the *syn* isomer, while not influencing the corresponding protons in the *anti* isomer. By analogy, the broad multiplet centered at 2.94 ppm (1.5 H, $W_{1/2}$ = 52 Hz) was assigned to the unaffected C3′ methylene protons of the **8a-*anti*** isomer. The C3′ methylene protons of the **8a-*syn*** isomer, coming under the shielding effect of the phenylimino group, are seen as a broad hump centered at about 2.42 ppm (0.5 H), under the upfield slope of the broad multiplet centered at 2.47 ppm, assigned to one of the protons on the C4′-carbon atom. The chemical shift difference of 0.52 ppm between the *syn* and *anti* C3′-methylene protons in **8a** is entirely consistent with the observed and calculated values.[7] From the ratio of the peaks at 2.42 and 2.94 ppm, it is concluded that the **8a-*anti*** and **8a-*syn*** isomeric forms are present in the ratio of 3:1. The preponderance of the *anti* form is readily explained by comparing the van der Waals radius of oxygen atom (1.4 Å) with that of the methylene group (2.0 A).[12] The second proton on the C-4′ carbon atom appeared as a multiplet at 2.07 ppm, and the peaks at 3.22 and 3.39 ppm, that constitute the AB part of an ABX system, are due to the methylene protons of the CH_2I group. The C4′ and C6′ methylene resonances are each split into two resonance due to the presence of the asymmetric C5′-carbon atom. The C-5′-methine proton is seen as a broad multiplet centered at 4.62 ppm (1.0 H) and the ester methyls at 3.96 ppm (6 H).

Noteworthy in Figure 1a is the broadness of all the peaks and this can be attributed to the slow rate of conformational inversion processes occurring in the dihydro-2(3*H*)-furanylidene ring system, because of substitution by the bulky iodomethyl and triiodophenylimino moieties. However, the increased broadness of the peaks ascribed to the C3′ methylene protons can only be explained by postulating that the *anti* and *syn* forms of the cyclic-imidate **8a** undergo slow interconversion in the

(12) Pauling, L. *The Nature of the Chemical Bond*, 3rd ed.; Cornell Univ. Press: Ithaca, NY, 1960; pp 261–262.

NMR time scale. To test this hypothesis, we repeated the NMR study at 55 °C (Figure 1b). The peaks at 2.07 (1.0 H) and 2.47 ppm (1.0 H), assigned to the C-4′-methylene protons, now appeared as well resolved sextuplets, and the peaks at 3.22, 3.39, and 4.62 ppm were also better resolved. The peak at 2.42 ppm, assigned to the *syn* C3′-methylene protons, completely disappeared and there was a broad peak at 2.85 ppm (2.0 H, $W_{1/2}$ = 88 Hz) assignable to both the *syn* and *anti* C3′ methylene protons. These changes mean that the environments of the C3′ methylene protons in the two isomers **8a-*anti*** and **8a-*syn*** are sufficiently averaged to cause them to coalesce at 55 °C. It has been reported[13] that simple imidates, such as methyl *N*-methylacetimidate, exist only in the *anti* form and that *syn*−*anti* interconversion is not observed. However, there is also a report[14] on imidates that undergo interconversion depending upon substitution.

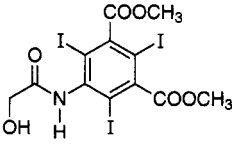
We now turn to an explanation of the likely role of strong bases in redirecting the course of the iodocyclization reaction. A review of iodocyclization literature[5] reveals that formation of iodolactones from unsaturated amides and iodolactams from silylated unsaturated amides is the normally expected outcome. However, under special circumstances oxygen cyclization leading to the 2(3*H*) furanylideneamino ring system has been reported. These consist of employing basic aqueous media,[15] $AgBF_4$[16] on ω-bromoalkanoic acid amides, or of resorting to selenocyclization[17] of ω-unsaturated alkanoic acid amides. A likely explanation for the high degree of base mediated selectivity in the case of **6a** could rest in the greater acidity (reported[18] pK_a 11) of triiodoanilides than simple anilides. Hence, in strongly basic media (0.1 M NaOH), **6** could be expected to exist predominantly in its conjugate base form, which is known[19] to promote alkylation on nitrogen in amides. If this argument were true, we may speculate that the ratio of nitrogen versus oxygen cyclization could depend on the extent of ionization. Verification was provided when we found that on going from 0.1 M NaOH to 1.0 M K_2CO_3 the ratio of **10a** to **8a** changed from 24:1 to 3:1.

The NIS-mediated iodocyclization reaction was next applied to the pentenoylanilide **6b** or **6c**. Treatment of these two anilides with NIS (1.33 equiv) in chloroform at 50 °C afforded the 2-furanylideneamino **8b** or **8c** in 80% and 79% yields, respectively. The spectral and elemental analysis data were in complete agreement with the structures assigned. As expected, NMR spectra indicated that **8b** and **8c** are present as a mixture *syn* and *anti* isomers. Most of the peaks were split into multiplets due to the presence of a larger number of isomers in **8b** and **8c** than in the case of **8a**, arising from stereo-, geometrical, and atropoisomerism in triiodoisophthalamides.[20]

Based on our experience in the ring closure chemistry of the dimethyl ester **6a**, extension of the iodocyclization methodology to obtain the pyrrolidinones **10b** and **10c** required the use of a strong base. In this context the presence of base sensitive acetyl groups in **6b** and **6c** posed a problem. Since these two starting materials were readily available, we found it more expedient to adopt the strategy of deliberately deacetylating **6b** and **6c**, carrying out the iodocyclization under basic conditions, and then reinstating the acetyl groups. Toward this end **6b** and **6c** were exposed to a catalytic amount of sodium methoxide in methanol and then treated with NIS (3 equiv) in aqueous methanol containing NaOH to direct the ring closure toward nitrogen participation. The iodocyclized products obtained were reacetylated employing acetic anhydride in pyridine. As anticipated the major products, formed in about 64% yield in each case, were the (iodomethyl)pyrrolidinones **10b** and **10c**, respectively. NMR and mass spectral data were in full agreement with the assigned pyrrolidinone structure.

Synthesis of 6-(Iodomethyl)-1,4-dioxan-2-ylideneamine 9a and 3-(Iodomethyl)morpholin-5-one 11 Derivatives. The six-membered heterocycles **9** and **11** were synthesized by taking recourse to the NIS-mediated iodocyclization of the (allyloxy)acetanilides **7**. Treatment of **7a** with NIS (2.0 equiv) in chloroform at room temperature for 15 h afforded a mixture of products. The major product formed in 50% yield was the 2-imino-1,4-dioxane **9a**. NMR and mass spectral data were in agreement with the structure assigned. To our knowledge, the 1,4-dioxan-2-ylideneamine ring system present in compound **9a** has so far not been reported.

Two side products identified in the above reaction mixture were the aniline **3a** and the α-hydroxy acetanilide **20** formed in 3.7% and 16% yields, respectively. The former was identified by coinjection with an authentic sample in HPLC and the latter by acylation of the aniline **3a** with (acetyloxy)acetyl chloride followed by deacetylation. The formation of **20** is rationalized as being due to the allylic iodination of **7a** by NIS, followed by spontaneous hydrolysis of the α-iodo ether intermediate formed, during aqueous workup. It is believed that **3a** results by the hydrolytic cleavage of the 2-imino-1,4-dioxane **9a** under the acidic conditions of the aqueous workup, because of the liberation of HI during the hydrolytic step proposed for the formation of **20**.



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As expected the strong base-promoted iodocyclization of **7a** proceeded near exclusively by nitrogen participative attack. Treatment of **7a** with NIS (2.27 equiv) in dioxane−methanol solution in the presence of NaOH (2 equiv) furnished the 3-(iodomethyl)morpholin-5-one **11a**

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

in 83% yield. The presence of an AB quartet at 4.36 ppm assignable to the $OCH_2C(=O)$ protons in the ^{1}H-NMR spectrum and the presence of peaks at 5.3 (CH_2I) and 62.4 ppm [N(Ar)CH] in the ^{13}C-NMR spectrum supported the assigned structure.

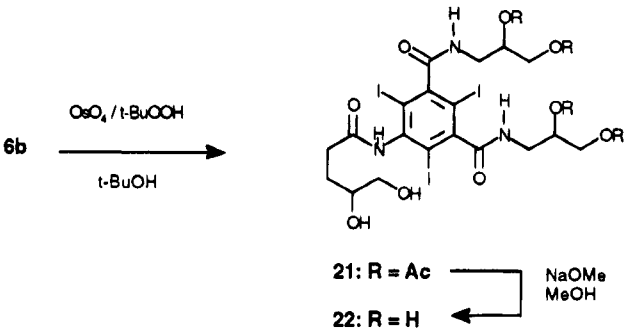
The NIS-mediated iodocyclization reaction was next applied to the (allyloxy)acetanilides **7b** and **7c** again employing the deacetylation, iodocyclization, and reacetylation strategy. Compound **7b** and **7c** were separately treated with a catalytic amount of sodium methoxide in methanol, followed by NIS (2.5 equiv) in dioxane–methanol–water medium containing NaOH and finally with acetic anhydride in pyridine. As anticipated, the major products isolated after silica gel column chromatography in 62 and 63% yields, respectively, were the (iodomethyl)morpholinones **11b** and **11c**.

Conversion of the Iodomethyl Derivatives into the Hydroxymethyl Derivatives. Acetolysis[21] of the iodomethyl derivatives to the corresponding (acetyloxy)-methyl derivatives was achieved generally by refluxing with silver acetate in acetic acid. Thus, the iodomethyl derivatives **8a**, **8b**, **8c**, **10b**, **11a**, **11b**, and **11c** afforded the (acetyloxy)methyl analogs **12a**, **12b**, **12c**, **14b**, **15a**, **15b**, and **15c** in 80–92% yields. The displacement of the iodo group by the acetyloxy group could also be achieved by treatment with tetraethylammonium acetate (TEAA). Thus, **10a** and **10c** furnished the acetates **14a** and **14c** in 77% and 84% yields, respectively, when refluxed with TEAA in dioxane or CH_3CN. The employment of the basic conditions of TEAA usage was, however, not an efficient general acetolysis method as exemplified by the observation that **8a**, when treated with TEAA in dioxane, provided **12a** in only 45% yield, along with the elimination product **13a** in 50% yield. The structure for **13a** is based on its ^{13}C-NMR spectrum that exhibited signals at 87.8 ppm for the exocyclic methylene and at 158.5 ppm for the 5-olefinic carbon atom.[22]

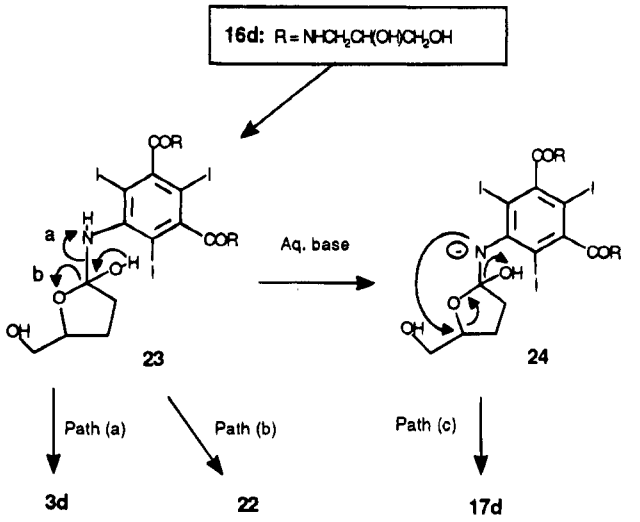
Deacetylation of the peracetylated derivatives **12b**, **12c**, **14b**, **14c**, **15b**, and **15c** by the transesterification method using catalytic amounts of sodium methoxide in dry methanol at room temperature furnished the pentahydroxy derivatives **16d**, **16e**, **17d**, **17e**, **18d**, and **18e**, respectively, in near quantitative yields. The purity of these products at this stage was generally around 98% by HPLC analysis. Further purification by low pressure reversed phase column chromatography over CHP-20 resin[23] using 5–10% aqueous EtOH as eluent afforded the desired end products of purity >99.9%. The spectral as well as other analytical data on the (acetyloxy)methyl and hydroxymethyl derivatives were in complete agreement with the structures assigned to them. As expected ^{1}H-NMR data revealed that compounds **12b**, **12c**, **16d**, and **16e** existed as a mixture of *anti* and *syn* isomers. All the compounds containing the triiodoiosphthalamide skeleton exhibited more complicated NMR patterns than the compounds belonging to the dimethyl ester series, due to the greater number of atropoisomers and geometrical isomers possible in triiodoisophthlamides.[20]

Hydrolytic Stability of 16d, 17d, and 18d. High water solubility and hydrolytic stability in aqueous solution are prime prerequisites for injectable NICM solutions. In this context we investigated the hydrolytic stability of the water soluble compounds **16d**, **17d**, and **18d** by heating aqueous solutions at 100 °C over a 24 h period at neutral pH. Compounds **16d** and **17d** were resistant to hydrolytic degradation, while the imidate **16d**, not unexpectedly, underwent ready cleavage. The homogeneity index of the imidate **16d** by HPLC analysis was only 90.4% at 24 h and two decomposition products **3d** and **22** (Scheme 2) were detectable to the extent of 2.8% and 6.8%, respectively. Characterization of one of the decomposition products as **3d** was accomplished by demonstrating that it coeluted with an authentic specimen prepared by the deacetylation of **3b** and that its molecular weight was 705 as per LC-MS data. Characterization of the other as **22** rested on demonstrating that it coeluted with an authentic sample prepared from the anilide **6b** by hydroxylation of the double bond by treatment with *tert*-butyl hydroperoxide in the presence of OsO_4 to obtain the diol **21**, followed by its deacetylation with sodium methoxide in methanol. The formation of these two products is readily understood based on the current understanding of the hydrolytic mechanisms of imidates.[24] Addition of water to the C=N bond of the imino ether **16d** furnishes initially the tetrahedral intermediate **23** (see Scheme 3), which breaks down by either C–N bond cleavage (path a) to afford **3d** or by C–O bond cleavage (path b) to give **22**. At pH 6 these two processes are not efficient as reflected by the low yields. Reflecting the better leaving group ability of OR over NH-(R), the preference of path b over path a is approximately 2:1.

Scheme 2



Scheme 3



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(23) Procured from Mitsubishi Corp., New York, NY.

(24) See ref 14b, pp 445–447.

In a more detailed hydrolytic study, the nature and extent of the decomposition of the imino ether **16d** at 85 °C was found to be pH dependent. At pH 6 after 24 h compound **16d** remained unaltered to the extent of 99.2%, affording **3a** and **22** in HPLC yields of about 0.4% each. At pH 2 over a period of 30 min, only 2% of **16d** remained unchanged, the decomposition products **3d** and **22** being formed in HPLC peak ratios of 80% and 18%, respectively. This is not in agreement with the earlier observation[25] that hydrolysis of imidates derived from very weakly basic amines, such as di- and trinitroanilines, produce increasing yields of the amine as pH is increased. We must conclude that the triiodoanilines as a class are not as weakly basic as di- and trinitroanilines.

At pH 12 during 24 h, 60.9% of **16d** remained unchanged, with the formation of three products, two of which were identified as **3d** and **22** in HPLC yields of 13.6% and 0.5%, respectively. The third and major product, formed in a HPLC yield of 24.3%, was identified as the lactam **17d** by demonstrating that it coeluted with an authentic sample in reversed phase HPLC and that its molecular weight was 803 as evidenced by LC-MS data. The formation of the lactam **17d** from the imino ether **16d** is reminiscent of the Chapman rearrangement.[26] It is tempting to speculate that its occurrence at high pH might arise from the greater acidity of the NH proton (expected[18] pK_a ~11) than that of the OH proton in the intermediate **23**. The conjugate base **24**, thus generated, could undergo rearrangement by path c yielding the lactam **17d**. Obviously careful kinetic measurements are necessary to pronounce on the exact mechanisms involved at the pH ranges studied.

Conclusions

Employing a NIS-mediated intramolecular iodocyclization strategy on pentenoylanilides **6** and (allyloxy)-acetanilides **7**, we have been able to demonstrate the formation of dihydro-2(3*H*)-furanylideneamines **8** and 1,4-dioxan-2-ylideneamines **9**, respectively, by amide-oxygen participative nucleophilic attack. If a strong base is present, the mode of ring closure is diverted to one of predominant amide-nitrogen participative nucleophilic attack, leading to (iodomethyl)pyrrolidinones **10** and (iodomethyl)morpholinones **11**, respectively. The 1,4-dioxan-2-ylideneamine ring system in **9** is new. The intermediacy of the corresponding conjugate bases formed from **6** and **7** under alkaline conditions and their preference to undergo amide-nitrogen participative iodocyclization are invoked to rationalize the results obtained. The products **8** and **9** exist as an interconverting mixture of *syn* and *anti* isomers about the C=N double bond, in which the *anti* isomer predominates. Acetolysis of the iodocyclized products followed by deacetylation provided the final products **16**–**18** that are of interest as water soluble X-ray contrast agents.

The new candidates were evaluated for their potential to serve as X-ray diagnostic agents. The furanylideneamino **16d** did not have the high hydrolytic stability required of contrast media. The lactams **17** and **18**, however, possessed acceptable stability. Aqueous 1 M solutions of all the new heterocyclic polyhydroxytriiodoisophthalamides, as expected,[1] possessed lower osmolality than those of Iopamidol (**1**) and Iohexol (**2**). The viscosity values were comparable. The water solubility of the candidates **16d**, **17d**, and **18d**, possessing the 2,3-dihydroxypropyl side chain on the isophthalamide nitrogen atoms, was in the acceptable range (>80%), while compounds **17e** and **18e**, possessing the 2-hydroxy-2-(hydroxymethyl)ethyl side chain, had very poor water solubility. The only exception in the 2-hydroxy-2-(hydroxymethyl)ethyl side chain series was **16e**, whose high water solubility could arise from the fact that it exists as a mixture of *anti* and *syn* isomers. Similarly, it is likely that the presence of several asymmetric centers in **16d**, **17d**, and **18d** contributes to some degree to the inability to form insoluble crystalline hydrates. The heterocyclic candidates described herein exhibited an unexpected property of prolonging the blood clotting time, a property desirable[27] in a contrast medium, but that is lacked by NICM, such as **1** and **2**, that are currently in clinical use.

Experimental Section

Melting points are uncorrected. Infrared spectra were obtained on KBr pellets. ^{1}H NMR and ^{13}C NMR are at 270 and 75.5 MHz, respectively, and are given in δ values. All assignments made in the ^{13}C-NMR spectra were verified by INEPT experiments. HPLC analyses were carried out, unless otherwise specified, with a reverse phase C8-silica column (5 mm, 4.6 mm × 15 cm) using CH_3CN/H_2O 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.

General Procedure for the Acylation of Amines 3a–c. To a stirred solution of the amine **3** (50 mmol) in dimethylacetamide (DMA) (100 mL) was added the acid chloride **3** or **4** (1.5–2 0 equiv) slowly at 5 °C. After the addition, the mixture was stirred at 5 °C for 0.5 h and then at room temperature for 15–20 h. The progress of the reaction was monitored by TLC or HPLC. When the reaction was completed, DMA and other volatiles were removed *in vacuo* at 35–40 °C and the residue was dissolved in EtOAc (250 mL). The solution was washed successively with water, aqueous $NaHCO_3$, water, and saturated NaCl solution. The organic layer was dried and the solvent removed to obtain the crude anilide **6** or **7**. Purification by crystallization from hexane/EtOAc or by column chromatography over silica gel (hexane/EtOAc) furnished the pure anilides **6** or **7**. The following anilides were prepared.

Dimethyl 2,4,6-Triiodo-5-[(1-oxo-4-pentenoyl)amino]-1,3-benzenedicarboxylate (6a). Starting from **3a** (11.74 g, 20 mmol) and 4-pentenoyl chloride (**4**) (4.72 g, 40 mmol), the anilide **6a** was obtained as white needles (10.9 g, 88%) after crystallization from EtOAc/hexane (5:1): mp 193–194 °C; TLC R_f 0.57 (EtOAc/hexane 1:1); HPLC t_R 4.9 min (CH_3CN/H_2O 7:3); UV (MeOH) λ_{max} 241 nm (ϵ 31 389); IR 3450, 1731, 1718, 1651, 1511, 1219 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.52 (m, 4H), 3.96 (m, 6H), 5.03 (d, 1H, J_{cis} = 10.4 Hz), 5.13 (d, 1H, J_{trans} = 17.6 Hz) 5.86–5.96 (m, 1H) 7.99 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 28.6, 34.7, 53.3, 88.2, 100.1, 115.3, 137.4, 144.2, 147.4, 168.5, 170.1; MS *m/z* 670 (MH^+), 544, 351, 135. Anal. Calcd for $C_{15}H_{14}I_3NO_5$: C, 26.93; H, 2.11; I, 56.91; N, 2.09. Found: C, 26.94; H, 1.88; I, 56.77; N, 2.05.

***N,N'*-Bis[2,3-bis(acetyloxy)propyl]-2,4,6-triiodo-5-[(1-oxo-4-pentenoyl)amino]-1,3-benzenedicarboxamide (6b).** Starting form **3b** (21.8 g, 25 mmol) and **4** (7.44 g, 62 mmol), pure **6b** was obtained as a fine powder (21.3 g, 89%) after crystallization from EtOAc/hexane: mp 225–227 °C; TLC R_f 0.50 (EtOAc/hexane); HPLC t_R 5.8 min (CH_3CN/H_2O 7:3); UV (MeOH) λ_{max} 241 nm (ϵ 30 942); IR 3264, 1740, 1655, 1544, 1228 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.02 (s, 12H), 2.38–2.40 (m, 4H), 3.35–3.60 (m, 4H), 4.15–4.40 (m, 4H), 4.95–5.18 (m, 4H), 5.85–6.00 (m, 1H), 8.40–8.92 (4 t, 2H), 9.85 (s, 1H); ^{13}C NMR

(25) Okuyama, T.; Pletcher, T. C.; Sahn, D. J.; Schmir, G. L. *J. Am. Chem. Soc.* **1973**, *95*, 1253.
(26) See ref 14b, pp 551–559.
(27) Dawson, P. *Invest. Radiol.* **1988**, *23* (Suppl 2), S310.

(DMSO-d_6) δ 20.6, 21.0, 27.9, 34.5, 39.8, 62.6, 68.7, 89.7, 98.7, 114.8, 137.4, 143.2, 150.0,169.0, 170.3, 170.7, MS m/z 956 (MH^+), 830, 653. Anal. Calcd for $C_{27}H_{32}I_3N_3O_{11}$: C, 33.95; H, 3.38; I, 39.85; N, 4.40. Found: C, 33.94; H, 3.24; I, 39.68; N, 4.30.

***N,N'*-Bis[2-(Acetyloxy)-1-[(acetyloxy)methyl]ethyl]-2,4,6-triiodo-5-[(1-oxo-4-pentenyl)amino]-1,3-benzenedicarboxamide (6c).** Starting from **3c** (47.75 g, 50 mmol) and **4** (11.9 g, 100 mmol), pure **6c** (42.5 g, 81%) was obtained after crystallization from acetone/hexane (3:1): mp 262–264 °C; UV (MeOH) λ_{max} 241 nm (ϵ 30 942); IR 3264, 1733, 1652, 1546, 1243 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.03 (s, 12H), 2.38–2.41 (m, 4H), 4.13–4.22 (m, 4H), 4.30–4.40 (m, 2H), 4.98–5.14 (m, 2H), 5.92–6.10 (m, 1H), 8.80 and 8.92 (dd, 2H), 9.94 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 20.7, 28.8, 34.8, 47.0, 62.0, 89.7, 99.2, 99.3, 115.1, 137.6, 143.3, 149.5, 169.1, 169.8, 170.2; MS m/z 956 (MH^+), 830, 653. Anal. Calcd for $C_{27}H_{32}I_3N_3O_{11}$: C, 33.95; H, 3.38; N, 4.40; I, 39.85. Found: C, 33.93; H, 3.18; N, 4.22; I, 39.84.

Dimethyl 2,4,6-Triiodo-5-[[(2-propenyloxy)acetyl]amino]-1,3-benzenedicarboxylate (7a). Starting from **3a** (2.95 g, 5 mmol) and (allyloxy)acetyl chloride (**5**) (1.0 g, 7.5 mmol), pure **7a** was obtained as white needles (3.02 g, 93%) after crystallization from EtOAc/hexane (3:1): mp 179–180 °C; TLC R_f 0.51 (hexane/EtOAc 3:2); HPLC t_R 5.6 min (CH_3CN/H_2O 7:3); UV (MeOH) λ_{max} 241 nm (ϵ 32 365); IR 1733, 1690, 1484, 1337, 1232 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.97 (s, 6H), 4.15 (s, 2H), 4.23 (d, 2H, J = 5.87 Hz), 5.30 (dd, 1H, J_{gem} = 1.18 Hz, J_{cis} = 9.96 Hz), 5.39 (dd, 1H, J_{gem} = 1.18 Hz, J_{trans} = 17.3 Hz), 5.96 (m, 1H), 8.32 (bs, 1H); ^{13}C-NMR ($CDCl_3$) δ 53.4, 69.5, 72.8, 86.7, 96.8, 118.5, 133.0, 142.0, 148.5, 167.8, 167.9; MS m/z 686 (MH^+). Anal. Calcd for $C_{15}H_{14}I_3NO_6$: C, 26.30; H, 2.06; I, 55.58; N, 2.05. Found: C, 26.33; H, 2.14; I, 55.87; N, 1.94.

***N,N'*-Bis[2,3-bis(acetyloxy)propyl]-2,4,6-triiodo-5-[{(2-propenyloxy)acetyl}amino]-1,3-benzenedicarboxamide (7b).** Starting from **3b** (22.69 g, 26 mmol) and **5** (4.0 gm, 30 mmol), pure **7b** was obtained as a white foamy solid (19.84 g, 77%) after flash chromatography over silica gel (EtOAc/ hexane): TLC R_f 0.36 (EtOAc/hexane 3:1); HPLC t_R 6.0 min (CH_3CN/H_2O 1:1); UV(CH_3CN) λ_{max} 241 nm (ϵ 29 430); IR 3403, 1736, 1664, 1543, 1372,1244 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.06 (s, 12H), 3.65 (bd, 4H), 4.13 (s, 2H), 4.25 (d, 4H, J = 6 Hz), 4.41 (d, 2H, J = 10 Hz), 5.21 (bs, 2H), 5.27 (d, 1H, J = 11 Hz), 5.39 (d, 1H, J = 17 Hz), 5.98 (m, 1H), 7.29, 7.65, 7.75 (bp, 2H), 9.09, 9.50 (1H); ^{13}C NMR ($CDCl_3$) δ 20.7, 21.2, 39.8, 63.5, 69.4, 70.1, 72.8, 88.3, 97.8, 118.2, 133.7, 142.4, 149.5, 149.9, 168.8, 169.9, 170.4, 170.7; MS m/z 972 (MH^+), 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. Found: C, 33.01; H, 3.28; I, 39.29; N, 4.12.

***N,N'*-Bis[2-(acetyloxy)-1-[(acetyloxy)methyl]ethyl]-5-[[(2-propenyloxy)acetyl]amino]-2,4,6-triiodo-1,3-benzenedicarboxamide (7c).** Starting from **3c** (30 g, 34 mmol) and **5** (9.0 gm, 67 mmol), **7c** was obtained as a white amorphous solid (32.1 g, 97%, purity 98%), after flash chromatography over silica gel (EtOAc/hexane). An analytical sample was obtained by crystallization from aqueous methanol: mp 225–226 °C; TLC R_f 0.45 (5% MeOH in $CHCl_3$); HPLC t_R 6.6 min (CH_3CN/H_2O 1:1); UV (CH_3CN) λ_{max} 241 nm, (ϵ 29 130); IR 1726, 1670, 1541, 1367, 1245, 1049 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.06 (s, 12H), 4.10 (s, 2H), 4.23 (s, 8H), 4.54 (bs, 2H), 5.28 (d, 1H, J = 10.5 Hz), 5.39 (d, 1H, J = 18.7 Hz), 5.99 (m, 1H), 6.94,7.40 (2bs 1H), 8.77, 9.05 (2 s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0, 47.9, 62.3, 69.5, 72.8, 88.2, 97.7, 98.1, 118.2, 133.6, 142.7, 149.4, 168.4, 169.0, 170.7; MS m/z 972 (MH^+), 930, 912, 870, 846, 797, 755, 699, 669, 642, 629, 543. Anal. Calcd for $C_{27}H_{32}N_3I_3O_{12}$: C, 33.39; H, 3.15; I, 39.2; N, 4.33. Found: C, 33.17; H, 3.15; I, 39.43; N, 4.17.

General Procedure for Iodocyclization under Non-basic Conditions. To a solution of the alkenylanilide **6a–c** (4 mmol) in $CHCl_3$ (30 mL) was added *N*-iodosuccinimide (NIS) (8 mmol) and the mixture stirred at 50 °C for 1 h. The progress of the reaction was monitored by TLC and/or HPLC. In the case of **7**, the reaction was done at room temperature overnight (12–15 h). When the reaction was completed, the solvent was removed and the residue was taken up in EtOAc (100 mL). The solution was washed successively with water (50 mL), aqueous $Na_2S_2O_3$ (10%, 25 mL), and water (50 mL), dried, and concentrated. Purification of the residue by flash chromatography over silica gel (eluent, EtOAc/hexane) furnished the furanylideneamine **8** (80–85%) or the dioxanylideneamine **9** (50%). The following compounds were prepared using this procedure.

Dimethyl 5-[[Dihydro-5-(iodomethyl)-2(3*H*)-furanylidene]amino]-2,4,6-triiodo-1,3-benzenedicarboxylate (8a). Starting from **6a** (2.67 g, 4 mmol) and NIS (1.8 g, 8 mmol), the imino-furan **8a** was obtained as a pale yellow glassy solid (2.52 g, 79%); TLC R_f 0.4 (EtOAc/hexane 1:2); HPLC t_R 6.7 min (CH_3CN/H_2O 7:3); UV (MeOH) λ_{max} 240 nm (ϵ 33 231); IR 3450, 1732, 1703, 1333, 1219 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.07 (m, 1H), 2.45 (m,1.5 H), 2.95 (bs, 1.5 H), 3.22 (bs, 1H), 3.39 (bs, 1H), 3.94 (s, 6H), 4.62 (bs, 1H); ^{13}C NMR ($CDCl_3$) δ 6.53, 28.9, 29.5, 53.2, 79.2, 82.4, 87.2, 147.4, 153.1, 165.7, 168.4; MS m/z 796 (MH^+), 670, 542. Anal. Calcd for $C_{15}H_{13}I_4NO_5$: C, 22.60; H, 1.65; I, 63.86; N, 1.76. Found: C, 22.71; H, 1.77; I, 64.20; N, 1.68.

***N,N'*-Bis[2,3-bis(acetyloxy)propyl]]-5-[[dihydro-5-(iodomethyl)-2(3*H*)-furanylidene]amino]-2,4,6-triiodo-1,3-benzenedicarboxamide (8b).** Starting from **6b** (14.3 g, 15 mmol) and NIS (4.48 g, 20 mmol), **8b** was obtained as a white amorphous solid (13.0 g, 80%): TLC R_f 0.47 (EtOAc); HPLC t_R 6.6 min (CH_3CN/H_2O 7:3); UV (MeOH) λ_{max} 240.6 nm (ϵ 34 721); IR 1737, 1670, 1234 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.85–2.15 (m, 1H), 2.05 (s, 12H), 2.20–2.45 (m, 1.4H), 2.90 (bp, 1.6H); 3.20–3.72 (bm, 6H), 4.15–4.40 (m, 4H), 4.62 (bp, 1H), 5.09 (bs, 2H), 8.45 (bs, 0.4H), 8.73 (bs, 1.6H); ^{13}C NMR (DMSO-d_6) δ 9.0, 20.5, 21.0, 28.4, 28.9, 38.6, 63.0, 69.4, 82.1, 82.2, 88.3, 148.9, 152.4, 164.5, 169.7, 170.1; MS m/z (MH^+), 1082, 907, 781. Anal. Calcd for $C_{27}H_{31}I_4N_3O_{11}$: C, 30.19; H, 2.94; I, 46.57; N, 3.86. Found: C, 30.15; H, 2.77; I, 46.25; N, 3.72.

***N,N'*-Bis[2-(acetyloxy)-1-[(acetyloxy)methyl]ethyl]-5-[[dihydro-5-(iodomethyl)-2(3*H*)-furanylidene]amino]-2,4,6-triiodo-1,3-benzenedicarboxamide (8c).** Starting from **6c** (9.55 g, 10 mmol) and NIS (4.48 g, 20 mmol), **8c** was obtained as a glassy solid (8.5 g, 78.5%): mp 145–150 °C dec; UV λ_{max} 241 nm (ϵ 34537); IR 1725, 1674, 1238 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.80–2.1 (m, 1H), 2.05 (s, 12H), 2.40 (m, 2H), 2.90 (m, 1H), 3.47 (m, 2H), 4.16 (s, 8H), 4.35 (m, 2H), 4.65 (m, 1H), 8.50 (m, 0.35H), 8.85 (m, 1.65H); ^{13}C NMR (DMSO-d_6) δ 9.5, 20.7, 28.4, 28.8, 46.8, 62.0, 80.5, 81.0, 82.2, 82.5,148.5 152.2, 164.5, 169.1, 170.1; MS m/z 1082 (MH^+), 956, 896, 781, 653, 527. Anal. Calcd for $C_{27}H_{31}I_4N_3O_{11}$: C, 29.99; H, 2.89; N, 3.89; I, 46.95. Found: C, 29.94; H, 3.14; N, 3.79; I, 47.30.

2,4,6-Triiodo-5-[[6-(iodomethyl)-1,4-dioxan-2-ylidene]-amino]-1,3-benzenedicarboxylic Acid, Dimethyl Ester (9a). Starting from **7a** (34 mg, 0.05 mmol), NIS (22 mg, 0.1 mmol), and $CHCl_3$ (2 mL) at room temperature overnight (15 h), a brown residue (48 mg) was obtained. HPLC analysis (reversed phase C-8 column, CH_3CN/H_2O (6:4), at a flow rate 1 mL/min) showed one major peak (peak A, 52.6%, t_R 6 min) and four minor peaks, of which two (peak B, 3.7%, t_R 4.5 min, peak C, 16%, t_R 4.0 min) were identified. The major component **9a** (peak A) was isolated as a white amorphous solid (20 mg, yield 50%) by preparative TLC on silica gel (EtOAc/hexane/MeOH 60:40:1); ^1H NMR ($CDCl_3$) δ 3.31 (d, 2H, J = 6.5 Hz), 3.98 (s, 6H), 4.11 (m, 2H), 4.46 (bs, 1H), 4.58 (bs, 2H); MS m/z 812 (MH^+), 684, 628, 551, 517, 501, 360, 332. Anal. Calcd for $C_{15}H_{13}I_3NO_6$ (810.9): C, 22.22; H, 1.62; I, 62.60; N, 1.73. Found: C, 22.35; H, 1.94; I, 62.38; N, 1.52.

The minor products were identified as **3a** and **20** by coinjection with authentic samples. When the reaction was carried out at 50–55 °C for 1 h, the HPLC ratios of **9a**, **3a** and **20** were 42%, 7.8%, and 14.3%, respectively.

General Procedure for Iodocyclization of 6 and 7 under Basic Conditions. Method A: To a solution of the alkenylanilide **6a** or **7a** (5 mmol) in 10–30% MeOH in dioxane (150 mL) was added aqueous NaOH (5 M, 5 mL). After stirring for 30 min, NIS (1.11g, 5 mmol) was added portionwise over a period of 15–30 min and the stirring continued for a further 30 min. Then, an additional amount of NIS (1.32 g, 6 mmol) was added in portions and the stirring continued until

the reaction was over as per TLC or HPLC. The reaction mixture was then quenched with 10% aqueous $Na_2S_2O_3$, the pH was adjusted to 6–7, and the solvents were removed. The residue was extracted with EtOAc (100 mL). The organic layer was washed with water, dried, and concentrated. The residue was recrystallized from EtOAc/hexane to obtain pyrrolidinone **10a** or morpholinone **11a**.

Method B: To a solution of the anilide **6b**, **6c**, **7b**, or **7c** (20 mmol) in anhydrous MeOH (200 mL) was added a solution of NaOMe (40 mmol) in MeOH (30 mL). The mixture was stirred for 4 h, by which time all the acetate groups were deacetylated. The solvent was removed and the residue was dissolved in aqueous MeOH (50%, 200 mL). NIS (60 mmol) was added portionwise and the mixture stirred for 15–40 h at room temperature or until the reaction was over as per HPLC. The pH of the solution was then adjusted to 6.5–7.0, and the solvents were removed *in vacuo* at 35–40 °C. The residue was azeotroped with pyridine. The brown residue was then reacetylated by treating with acetic anhydride (20 mL) and pyridine (150 mL) under stirring for 15–25 h. Excess pyridine and acetic anhydride were removed and the residue was dissolved in EtOAc (250 mL). The solution was washed successively with aqueous $Na_2S_2O_3$ (10%) and water. Removal of the solvent followed by flash chromatography over silica gel (EtOAc/hexane) gave the iodomethyl analog **10b**, **10c**, **11b**, or **11c**.

Method C: Same as method A, except that K_2CO_3 and H_2O were substituted for aqueous NaOH and MeOH.

Dimethyl 2,4,6-Triiodo-5-[2-(iodomethyl)-5-oxo-1-pyrrolidinyl]-1,3-benzenedicarboxylate (10a). (a) Following method A, starting from **6a** (3.35 g, 5 mmol), NIS (total 2.5 g, 11 mmol), and NaOH (5 M, 5 mL), **10a** was obtained as white needles (3.42 g, 86%): mp 198–200 °C; TLC R_f 0.43 (EtOAc/hexane 1:1); HPLC t_R 5.8 min (CH_3CN/H_2O 7:3); UV (MeOH) λ_{max} 244 nm (ϵ 30 249); IR 1735, 1699, 1520, 1392, 1228 cm^{-1}; ^1H NMR ($CDCl_3$) 2.13 (m, 1H), 2.62 (m, 3H), 3.18 (dd, 1H, J_{vic} = 4.0 Hz, J_{gem} = 11 Hz), 3.41 (dd, 1H, J_{vic} = 10 Hz, J_{gem} = 11 Hz), 3.97 (s, 3H), 3.99 (s, 3H), 4.52 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 6.7, 27.2, 30.2, 53.5, 61.5, 88.3, 95.7, 100.6, 143.3, 149.7, 167.7, 173.6; MS *m/z* 796 (MH^+), 764, 688. Anal. Calcd for $C_{15}H_{13}I_4NO_5$: C, 22.64; H, 1.64; I, 63.90; N, 1.76. Found: C, 22.92; H, 1.59; I, 63.54; N, 1.88.

(b) Following method C, starting from **6a** (33.5 mg, 0.05 mmol), NIS (45 mg, 0.2 mmol), and K_2CO_3 (69 mg, 0.5 mmol) and using a biphasic mixture of dioxane (1 mL) and water (0.5 mL) for 24 h, a crude product was obtained, HPLC analysis of which indicated that both the N-cyclized (**10a**) and O-cyclized (**8a**) products were formed in 3:1 ratio.

***N,N'*-Bis[2,3-bis(acetyloxy)propyl]-5-[2-(iodomethyl)-5-oxo-1-pyrrolidinyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (10b).** Following method B, starting from **6b** (19.1 g, 20 mmol) and NIS 13.5 g, 60 mmol), **10b** was obtained as a glassy solid (13.8 g, 64%): TLC R_f 0.5 (EtOAc/hexane 9:1); HPLC t_R 7.9 min (CH_3CN/H_2O 4:6); UV (MeOH) λ_{max} 547 nm (ϵ 29 565); IR 3433, 1724, 1676, 1535, 1240 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.90–2.20 (m, 1H), 2.05 (s, 12H), 2.25–2.70 (m, 3H), 3.20–3.70 (bm, 6H), 4.16–4.40 (m, 5H), 5.12 (m, 2H), 8.40–8.85 (3m, 2H); ^{13}C NMR (DMSO-d_6) δ 7.9, 8.8, 20.0, 20.5, 26.0, 26.6, 29.6, 39.2, 61.2, 61.9, 62.9 69.4, 91.2, 91.3, 97.4, 97.6, 101.9, 102.5, 142.5, 150.5, 150.6, 169.5, 169.8, 190.1, 172.9; MS *m/z* 1082 (MH^+), 1022, 956. Anal. Calcd for $C_{27}H_{31}I_4N_3O_{11}$: C, 29.99; H, 2.89, I, 46.95; N, 3.89. Found: C, 30.44; H, 2.86; I, 46.74; N, 3.60.

***N,N'*-Bis[2-(Acetyloxy)-1-[(acetyloxy)methyl]ethyl]-5-[2-(iodomethyl)]-5-oxo-1-pyrrolidinyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (10c).** Following method B, starting from **6c** (19.1 g, 20 mmol) and NIS (13.5 g, 60 mmol), **10c** was obtained as a glassy solid (13.8 g, 64%). HPLC analysis revealed that this material was contaminated with approximately 8–9% of O-cyclized product **8c**, which could not be removed. This material was used as such for conversion into **14c**.

Dimethyl 2,4,6-Triiodo-5-[3-(iodomethyl)-5-oxo-4-morpholinyl]-1,3-benzenedicarboxylate (11a). Following method A, starting form **7a** (1.03 g, 1.5 mmol) and NIS (0.67g, 3 mmol), **11a** was obtained as white needles (1.01 g, 83%), after crystallization from EtOAc/hexane; mp 216–218 °C; TLC R_f 0.51 (hexane/ EtOAc 3:2); HPLC t_R 6.1 min (CH_3CN/H_2O 7:3); UV (MeOH) λ_{max} 244 nm (ϵ 33 920); IR 1735, 1661, 1522, 1411, 1227 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.30–3.35 (2q, 1H, J_{gem} = 9.4 Hz), 3.7–3.8 (dd, 1H, J_{gem} 9.4 Hz), 3.93 and 3.95 (2m, 1H, J_{gem} 12.3 Hz); 3.99 (s, 3H), 4.00 (s, 3H), 4.15 and 4.19 (2m, 1H, J_{gem} = 12.3 Hz); 4.36 (ABq, 2H, J_{AB} = 17.1 Hz), 4.51 (bd, 1H, J_{vic} = 11 Hz); ^{13}C NMR ($CDCl_3$) δ 5.3, 54.9, 62.4, 68.0, 70.3, 89.8, 97.5, 101.0, 146.5, 150.9, 151.2, 166.9, 169.1; MS *m/z* 812 (MH^+), 780, 686, 654, 625, 526, 498, 478. Anal. Calcd for $C_{15}H_{13}I_4NO_6$ (810.857): C, 22.22; H, 1.62; I, 62.60 N, 1.73. Found: C, 22.23; H, 1.48; I, 62.78; N, 1.50.

***N,N'*-Bis[2,3-bis(acetyloxy)propyl]-2,4,6-triiodo-5-[3-iodomethyl)-5-oxo-4-morpholinyl]-1,3-benzenedicarboxamide (11b).** Following method B, starting from **7b** (10.7 g, 11 mmol) and NIS (5.6 g, 25 mmol), **11b** was obtained as a white amorphous solid (7.5 g, 62%), after silica gel chromatography (30–90% EtOAc in hexane): mp 168–170 °C; TLC R_f 0.43 (EtOAc/hexane 4:1); HPLC t_R 6.5 min (CH_3CN/H_2O 1:1); UV (CH_3CN) λ_{max} 244 nm (ϵ 30 000); IR 1725, 1676, 1534, 1373, 1242 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.03 (s, 6H), 2.04 (s, 6H), 3.39–3.66 (m, 4H), 4.17–4.38 (m, 9H), 5.09 (bs, 2H), 8.6 and 8.95 (2 m, 2H); ^{13}C NMR (DMSO-d_6) δ 5.2, 20.5, 21.0, 39.8, 60.3, 60.6, 62.9, 66.1 68.2, 69.4, 91.7, 91.9, 97.3, 97.5, 102.0, 102.1, 144.1, 144.2, 150.4, 150.7, 151.0, 165.1, 169.6, 169.8, 170.1; MS *m/z* 1098 (MH^+), 1056, 1038, 996, 972, 923, 912. Anal. Calcd for $C_{27}H_{31}I_4N_3O_{12}$: C, 29.56; H, 2.85; I, 46.27; N, 3.83. Found: C, 29.65; H, 2.75; I, 45.96; N, 3.45.

***N,N'*-Bis[2-(acetyloxy)-1-[(acetyloxy)methyl]ethyl]-2,4,6-triiodo-5-[3-(iodomethyl)-5-oxo-4-morpholinyl]-1,3-benzenedicarboxamide (11c).** Following method B, starting from **7c** (1.95 g, 2 mmol) and NIS (0.89 g, 4 mmol), **11c** was obtained as a white amorphous solid (1.38 g, 63%): mp 186–189 °C dec; TLC R_f 0.38 (5% MeOH in $CHCl_3$); HPLC t_R 5.6 min (CH_3CN/H_2O 45:55); UV (CH_3CN) λ_{max} 244 nm (ϵ 29,050); IR 1734, 1672, 1542, 1243, 1049 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 2.0–2.07 (4s, 12H), 3.25 (dd, 1H), 3.70 (dd, 1H), 3.85 (m, 1H), 4.08 (unresolved t, 1H), 4.10–4.30 (bp, 10H), 4.40–4.6 (m, 3H), 6.62 (d, 1H), 7.65 (1H); ^{13}C NMR ($CDCl_3$) δ 4.5, 20.9, 21.1, 47.6, 61.0, 62.3, 62.5, 66.5), 68.8, 90.2) 97.0, 101.0, 145.0, 150.5, 151.0, 166.0, 166.0, 166.4, 170.7, 170.8; MS *m/z* 1098 (MH^+),-1056, 1038, 1014, 996, 923, 912, 881, 844, 797, 768, 669. Anal. Calcd for $C_{27}H_{31}I_4N_3O_{12}$: C, 29.56; H, 2.85; I, 46.27; N, 3.83. Found: C, 29.82; H, 2.72; I, 46.01; N, 3.56.

General Procedure for the Conversion of Iodomethyl Analogs 8–11 into (Acetyloxy)methyl Analogs 12, 14, 15. Method A: To a solution of the iodomethyl compound in glacial AcOH was added AgOAc and the mixture was stirred at 80–135 °C (bath temperature) for 15–25 h or until the reaction was over as per HPLC or TLC. The insoluble material was filtered off and the filtrate concentrated *in vacuo*. The residue was dissolved in EtOAc (50–250 mL), and the solution was washed successively with water, aqueous $NaHCO_3$, and water and then dried over $MgSO_4$. Removal of the solvent, followed by purification of the resulting crude product by column chromatography over silica gel (hexane/EtOAc) furnished the desired (acetyloxy)methyl compound in 75–88% yield.

Method B: To a solution of the iodomethyl compound in dioxane or CH_3CN was added tetraethylammonium acetate (Et_4NOAc) and the mixture was stirred at 50–80 °C for 0.5–18 h or until the reaction was over as per HPLC or TLC. The solvent was removed *in vacuo* and the residue was dissolved in EtOAc (75–200 mL). The solution was washed with water and dried and the solvent removed. The crude product was purified by silica gel chromatography (hexane/EtOAc) of the residue to obtain the (acetyloxy)methyl analog **12–14** in 45–84% yield.

Dimethyl 5-[[5-[(Acetyloxy)methyl]dihydro-2(3*H*)-furanylidene]amino]-2,4,6-triiodo-1,3-benzenedicarboxylate (12a). Following method A, starting from **8a** (795 mg, 1 mmol), AgOAc(688 mg, 4 mmol), and AcOH (8 mL), **12a** was obtained as a light pink glassy solid (580 mg, 80%): TLC R_f 0.35 (hexane/EtOAc 1:1); HPLC t_R 5.8 min (CH_3CN/H_2O 7:3); UV λ_{max} 240 nm (ϵ 32 933); IR 1735, 1698, 1334, 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (m, 1H), 2.06 (s, 3H), 2.30 (m, 1.5H),

2.86 (m, 1.5H), 3.96 (s, 6H), 4.05-4.30 (m, 2H), 4.86 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 20.4, 22.6, 28.3, 53.5, 63.5, 81.1, 82.2, 82.4, 98.5, 98.7, 147.4, 155.3, 167.7, 168.3, 170.1; MS m/z 728 (MH^+), 696, 602. Anal. Calcd for $C_{17}H_{16}I_3NO_7$: C, 28.08; H, 2.22; I, 52.37; N, 1.93. Found: C, 28.11; H, 2.20; I, 52.37; N, 1.90.

5-[[5-[(Acetyloxy)methyl]dihydro-2-(3*H*)-furanylidene]-amino]-*N,N'*-bis(acetyloxy)propyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (12b). Following method A, starting from **8b** (16.32 g, 15 mmol), AgOAc (10.01 g, 60 mmol), and AcOH (165 mL), **12b** was obtained as a light pink solid (13.2 g, 88%): TLC R_f 0.35 (EtOAc); HPLC t_R 5.8 min (CH_3CN/H_2O 7:3); UV (MeOH) λ_{max} 240 nm (ϵ 35 117); IR 1740, 1674, 1542, 1371, 1235 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.10 (bs, 16H), 2.35 (m,1.4), 2.92 (bp, 1.6 H); 3.35−3.72 (m, 4H), 4.05−4.50 (m, 6H), 4.90 (bs, 1H); 5.18 (bs, 2H), 8.40−8.95 (2m, 2H); ^{13}C NMR δ 20.4, 20.96, 24.5, 28.1, 28.7, 39.8, 63.2, 64.8, 69.7, 80.6, 81.5, 82.9, 88.7, 89.2, 149.4, 153.5, 165.5, 170.0, 171.0; MS m/z (MH^+) 1014, 888, 839, 762, 713. Anal. Calcd for $C_{29}H_{34}I_3N_3O_{13}$: C, 34.37; H, 3.38; I, 37.57; N, 4.15. Found: C, 34.37; H, 3.53; I, 37.88; N, 4.17.

***N,N'*-Bis[2-(acetyloxy)-1-[(acetyloxy)methyl]ethyl]-5-[[5-[(acetyloxy)methyl]dihydro-2(3*H*)-furanylidene]amino]-2,4,6-triiodo-1,3-benzenedicarboxamide (12c).** Following method A, starting from **8c** (7.5 g, 6.93 mmol), AgOAc (3.34 g, 20 mmol), and AcOH (100 mL), **12c** was obtained as a pink glassy solid (5.5 g, 78.6%); mp 172−175 °C; UV λ_{max} 240 nm (ϵ 32 719); IR 1726, 1674, 1242, 1049 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.04 (s, 15H), 1.90−2.20 (m, 1H), 2.28 (m, 2H), 2.84 (m, 1H), 4.15 (s, 10H); 4.34 (m, 2H), 4.83 (bs, 1H), 8.5 (m, 0.3H), 8.84 (m, 1.7H); ^{13}C NMR (DMSO-d_6) δ 20.7, 24.2, 28.7, 46.9, 62.0, 80.5, 80.9, 82.4,148.7,153.5, 165.5, 169.2, 170.1; MS m/z 1014 (MH^+), 888, 713. Anal. Calcd. for $C_{29}H_{34}I_3N_3O_{13}$: C, 34.37; H, 3.38; N, 4.15; I, 37.57. Found: C, 34.22; H, 3.50; N, 4.06; I, 37.82.

Dimethyl 5-[[5-Methylidenedihydro-2(3*H*)-furanylidene]amino]-2,4,6-triiodo-1,3-benzenedicarboxylate (13a). Following method B, starting from **8a** (795 mg, 1 mmol), Et_4NOAc (376 mg, 1.44 mmol), and dioxane (5 mL), a mixture consisting of mainly two products was formed. These were separated by flash chromatography over silica gel (hexane/EtOAc). The early eluting fractions contained the olefinic compound **13a** as a colorless solid (330 mg, 50%): TLC R_f 0.67 (hexane/EtOAc 1:1); HPLC t_R 7.4 min (CH_3CN/H_2O 7:3); UV (MeOH) λ_{max} 240 nm (ϵ 32,416); IR 1733, 1662, 1519, 1333 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.80−3.10 (m, 4H), 3.89 (s,6 H), 4.35 (bs, 1H), 4.67 (bs, 1H); ^{13}C-NMR (DMSO-d_6) δ 25.4, 25.6, 81.7, 88.6, 87.8, 146.9, 152.7, 158.4, 163.4, 168.1; MS m/z 668 (MH^+), 542. Anal. Calcd for $C_{15}H_{12}I_3NO_5$: C, 26.98; H, 1.95; I, 57.12; N, 2.09. Found: C, 27.19; H, 1.65; I, 56.84, N, 2.09.

The later eluting fractions contained a more polar product having properties identical with those of **12a** (300 mg, 45%) described above.

Dimethyl 5-[2-[(Acetyloxy)methyl]-5-oxo-1-pyrrolidinyl]-2,4,6-triiodo-1,3-benzenedicarboxylate (14a). Following method B, starting from **10a** (795 mg, 1 mmol), Et_4NOAc (783 mg, 3 mmol), and dioxane (30 mL), **14a** was obtained as a white glassy solid (560 mg, 77%): TLC R_f 0.35 (hexane/EtOAc 1:1); HPLC t_R 4.4 (CH_3CN/H_2O 7:3); UV (MeOH) λ_{max} 243 nm (ϵ 32 968); IR 1734, 1404, 1227, 1131 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.91−2.14 (m, 1H), 2.4−2.7 (m, 3H), 3.98 (s, 3H), 3.96 (s, 3H), 4.18- 4.26 (m, 2H), 4.45−4.61 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 20.4, 22.6, 30.1, 53.4, 58.5, 65.9, 88.3, 95.7, 100.6, 144.7, 149.0, 167.8, 170.2, 173.5; MS m/z 728 (MH^+), 696; Anal. Calcd for $C_{17}H_{16}I_3NO_7$: C, 28.08; H, 2.22; I, 52.37; N, 1.93. Found: C, 28.17, H, 2.06; I, 52.41; N, 1.89.

5-[2-[(Acetyloxy)methyl]-5-oxo-1-pyrrolidinyl]-*N,N'*-bis(acetyloxy)propyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (14b). Following method A, starting from **10b** (13.2 g, 15 mmol), AgOAc (6.0 g, 35 mmol), and AcOH (165 mL), **14b** was obtained as a light pink glassy solid (8.5 g, 79%): TLC R_f 0.50 (EtOAc); HPLC t_R 4.1 min (CH_3CN/H_2O 4:6); UV (MeOH) λ_{max} 244 nm (ϵ 27 958); IR 3264, 1740, 1655,1544, 1228 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.80−2.06 (m, 17H), 2.15−2.62 (m, 2H), 3.10−3.62, 4.04−4.40 (m, 7H), 5.02−5.90 (m, 2H), 8.60−8.88 (3q, 2H); ^{13}C NMR (DMSO-d_6) δ 20.5, 21.0, 22.5, 22.9, 29.7, 39.2, 58.3, 58.4, 63.0, 64.6, 64.2, 69.4, 91.2, 91.3, 97.4, 97.6, 101.1, 101.3, 143.4, 143.7, 150.3, 150.6, 169.5, 169.6, 170.1, 173.0, 173.1; MS m/z 1014 (MH^+), 954. Anal. Calcd for $C_{29}H_{34}I_3N_3O_{13}$: C, 34.37; H, 3.38; I, 37.57; N, 4.15. Found: C, 34.19; H, 3.09; I, 37.23; N, 4.05.

***N,N'*-Bis[2-(acetyloxy)-1-[(acetyloxy)methyl]ethyl]-5-[2-[(acetyloxy)methyl]-5-oxo-1-pyrrolidinyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (14c).** Following method B, starting from **10c** (12 g, 11 mmol), Et_4NOAc (5.74 g, 22 mmol), and CH_3CN (150 mL), **14c** was obtained as a white amorphous solid (9.4 g, 83.6%): UV (MeOH) λ_{max} 244 nm (ϵ 27 958); IR 3264, 1740, 1655, 1544, 1228 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.80−2.15 (m, 2H) 2.05 (s, 15H), 2.20−2.70 (m, 2H), 4.13 (bs, 10H), 4.34 (m, 2H), 8.50−9.10 (5d, 2H); ^{13}C NMR (DMSO-d_6) δ 20.7, 22.5, 22.9, 29.8, 47.0, 58.3,58.4, 61.9, 64.6, 65.0, 91.2, 91.4, 97.6, 101.3, 101.2, 143.4, 143.6, 150.1, 150.2, 168.9, 169.0, 169.0, 170.2, 173.0,173.0; MS m/z 1014 (MH^+), 972, 954. Anal. Calcd for $C_{29}H_{34}I_3N_3O_{13}$: C, 34.37; H, 3.38; I, 37.57; N, 4.15. Found: C, 34.22; H, 3.50; I, 37.82; N, 4.06.

5-[3-[(Acetyloxy)methyl]-5-oxo-4-morpholinyl]-2,4,6-triiodo-1,3-benzenedicarboxylic Acid, Dimethyl Ester (15a). Following method A, starting from **11a** (811 mg, 1 mmol), AgOAc (500 mg, 3 mmol), and AcOH (15 mL), **15a** was obtained as a white fluffy solid (685 mg, 92%): TLC R_f 0.49 (hexane/EtOAc 2:3); HPLC t_R 4.8 min (CH_3CN/H_2O 7:3); UV (MeOH) λ_{max} 243 nm (ϵ 32 330); IR 1737, 1680, 1523, 1434, 1416, 1332, 1231, 1049, 987 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.96 (s, 3H), 3.98 (s, 3H), 3.99 (s, 3H), 4.03 (m, 1H), 4.14 (2q, 2H), 4.39 (ABq, 2H, J_{AB} = 17.6 Hz), 4.40 (2q, 2H, J_{gem} = 7.9 Hz, J_{vic}= 3.5 Hz); ^{13}C NMR ($CDCl_3$) δ 20.6, 53.4, 53.5, 57.9, 63.5, 65.5, 68.7, 87.6, 95.6, 99.9, 145.9, 149.2, 149.4, 165.7, 167.7, 167.8, 170.1; MS m/z 744 (MH^+), 712, 628, 618, 586, 557, 490, 430. Anal. Calcd for $C_{17}H_{16}NI_3O_8$: C, 27.48; H, 2.17; I, 51.24; N, 1.89. Found: C, 27.60; H, 1.97; I, 51.51; N, 1.93.

***N,N'*-Bis[2,3-bis(acetyloxy)propyl]-5-[3{(acetyloxy)-methyl}-5-oxo-4-morpholinyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (15b).** Following method A, starting from **11a** (7.8 g, 7.1 mmol), AgOAc (4 g, 24 mmol), and AcOH (100 mL), **15b** was obtained as an amorphous solid (5.36 g, 73%); mp 210−212 °C; TLC R_f 0.24 (EtOAc/hexane, 4:1); UV (CH_3CN) λ_{max} 243 nm (ϵ 30 900); IR 1734, 1674, 1539, 1373, 1242, 1049 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.03 (3s, 15H), 3.30−3.60 (m, 4H), 3.85 (bs, 1H), 4.0−4.5 (m, 10H), 5.1 (bs, 2H), 8.65−8.95 (2H); ^{13}C NMR (DMSO-d_6) δ 20.5, 20.9, 39.5, 57.2, 61.0, 62.3, 62.9, 68.0, 69.6, 91.3, 97.5, 101.3, 145.0, 165.3, 170.0; MS m/z 1030 (MH^+), 988, 970, 946, 928, 904, 855, 844, 813, 802, 776, 729, 716, 700, 687, 573. Anal. Calcd for $C_{29}H_{34}N_3I_3O_{14}$: C, 33.84; H, 3.33; N, 4.08; I, 36.99. Found: C, 33.84; H, 3.27; N, 3.92; I, 37.03.

***N,N'*-Bis[2-(acetyloxy)-1-[(acetyloxy)methyl]ethyl]-5-[3- [(acetyloxy)methyl]-5-oxo-4-morpholinyl]-2,4,6-triiodo-1,3- benzenedicarboxamide (15c).** Following method A, starting from **11c** (2.01 g, 1.83 mmol), AgOAc (0.67 g, 4 mmol), and AcOH (35 mL), **15c** was obtained as a white solid (1.5 g, 82%); mp 208−210 °C; TLC R_f 0.35 (EtOAc/hexane 3:1); HPLC t_R 5.5 min (CH_3CN/ H_2O 1:1); UV (CH_3CN) λ_{max} 243 nm (ϵ 30 260); IR 1736, 1671, 1542, 1369, 1241, 1050 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.01 (s, 15H), 4.36 (bs, 10 H), 4.0−4.5 (m, 7H), 8.4−9.1 (m, 2H); ^{13}C-NMR (DMSO-d_6) δ 20.8, 47.1, 57.3, 62.2, 64.3, 64.6, 68.1, 91.4, 91.6, 97.5, 97.8, 101.1, 101.5, 145.1, 145.7, 150.1, 150.3, 150.6, 150.7, 165.4, 169.0, 170.0, 170.2; MS m/z 1030 (MH^+), 988, 970, 902, 855, 813. Anal. Calcd for $C_{29}H_{34}I_3N_3O_{14}$: C, 33.84; H, 3.33; I, 36.99; N, 4.08. Found: C, 33.73; H, 3.23; I, 37.12; N, 3.78.

General Procedure for the Deacetylation of the pentaacetates 12, 14, 15. To a solution of the pentaacetate (1−22 mmol) in anhydrous MeOH (10−150 mL) was added freshly prepared NaOMe (0.1−23 mmol, 0.2 equiv/acetate group) in MeOH (1−15 mL), and the mixture was stirred at room temperature for 1−4 h. The progress of the reaction was monitored by HPLC and when completed, the pH of the solution was adjusted to 6 by a slow addition of Dowex-50 (H^+) ion exchange resin. The resin was filtered off and the solvent removed to obtain the desired polyol in almost quantitative yield with a purity of 97−98% by HPLC analysis. In the case of **16a**, **17a**, and **18a**, further purification was done either by

crystallization from EtOAc/hexane or by silica gel column chromatography. The polyhydroxy compounds **16d**, **16e**, **17d**, **17e**, **18d**, and **18e** were purified by reversed phase column chromatography over nonionic CHP-20 resin using 1−10% EtOH in water as eluent. The fractions were monitored by HPLC, pure fractions were combined, and the solvents removed to obtain the desired product as a white amorphous solid. The isolated yields were in the range of 85−90% and the purity was >99.9%.

Dimethyl 5-[[Dihydro-5-(hydroxymethyl)-2(3*H*)-furanylidene]amino]-2,4,6-triiodo-1,3-benzenedicarboxylate (16a). Starting from **12a** (727 mg, 1 mmol), **16a** was obtained as a colorless glassy solid (620 mg, 90.5%): TLC R_f 0.45 (EtOAc/hexane 4:1); HPLC t_R 4.6 min (CH_3CN/H_2O 7:3); UV (MeOH) λ_{max} 240 nm (ϵ 31 373); IR, 3439, 1732, 1690, 1335, 1221 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.95 (m, 1H), 2.2 (m, 1.5H), 2.81(m, 1.5H), 3.50 (m, 2H), 3.88 (s, 6H), 4.58 (m, 1H), 4.97 (bs, 1H); ^{13}C-NMR (DMSO-d_6) δ 23.9, 29.8, 53.3, 63.6, 79.0, 84.8, 87.1, 147.5, 153.6, 166.9, 168.4; MS m/z 686 (MH^+). Anal. Calcd for $C_{15}H_{14}I_3NO_6$: C, 26.30; H, 2.06; I, 55.58; N, 2.05. Found: C, 26.78; H, 2.33; I, 55.28; N, 2.09.

[*N*,*N*′-Bis(2,3-dihydroxypropyl]-5-[[dihydro-5-(hydroxymethyl)-2(3*H*)-furanylidene]amino]-2,4,6-triiodo-1,3-benzenedicarboxamide (16d). Starting from **12b** (22.3 g, 22 mmol), **16d** was obtained as a colorless glassy solid. (15.95 g, 91%); TLC R_f 0.3 (EtOAc/MeOH 7:3); HPLC t_R 8.58 min (column, aminopropyl 4.6 mm × 25 cm; solvent, CH_3CN/H_2O (8:2) at a flow rate of 1 mL/min); UV (MeOH) λ_{max} 240 nm (ϵ 33 525); IR 3372, 3368, 1682, 1643 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.95 (m, 1H), 2.20 (m, 1.4H), 2.80 (m, 1.6 H), 3.05−3.80 (m, 12H), 4.32−5.20 (m, 6H), 8.00 (bs, 0.5H), 8.40 (bs, 1.5H); ^{13}C NMR (DMSO-d_6) δ 24.9, 29.3, 30.3, 43.3, 64.8, 64.1, 70.9, 85.9, 83.0, 83.5, 90.8, 149.5, 153.6, 165.7, 170.1; MS m/z (MH^+) 804, 713, 587. Anal. Calcd for $C_{19}H_{24}I_3N_3O_8 \cdot 1.6H_2O$: C, 27.38; H, 3.31; I, 45.68; N, 5.04. Found: C, 27.38, H, 2.97; I, 46.19; N, 4.92; H_2O, 3.64.

5-[[Dihydro-5-(hydroxymethyl)-2(3*H*)-furanylidene]-amino]-*N*,*N*′-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (16e). Starting from **12c** (2.7 g, 2.66 mmol), **16e** was obtained as white solid (1.85 g, 86%): mp 285−289 °C dec; UV λ_{max} 239 nm (ϵ 30 875); IR 3391, 3368, 1681, 1645, 1553, 1341, 1049 cm^{-1}; ^1H-NMR (DMSO-d_6) δ 1.95 (m, 1H), 2.17 (m, 1.4H); 2.78 (m, 1.6H), 3.52 (bs, 6H), 3.64 (bs, 4H), 3.83 (bs, 2H), 4.48−4.64 (bp, OH), 5.05 (m, 1H), 7.65 (bp, 0.4H), 8.19 (bs, 1.6H); ^{13}C NMR (DMSO-d_6) δ 23.7, 29.0, 29.1, 52.8, 59.7, 62.9, 81.7, 85.9, 88.9, 148.0 152.4, 169.8, 172.0, 175.6; MS m/z 804 (MH^+), 713, 678, 587, 552, 513, 459. Anal. Calcd for $C_{19}H_{24}N_3I_3O_8 \cdot 0.6H_2O$: C, 28.04; H, 3.12, N, 5.16, I, 46.58. Found: C, 28.15; H, 3.28, N, 5.21; I, 46.78; H_2O, 1.32.

Dimethyl 5-[2-(Hydroxymethyl)-5-oxo-1-pyrrolidinyl]-2,4,6-triiodo-1,3-benzenedicarboxylate (17a). Starting from **14a** (363 mg, 0.5 mmol), **17a** was obtained as colorless prisms (285 mg, 84%): mp 223−226 °C; TLC R_f 0.4 (EtOAc/hexane 8:2); HPLC t_R 3.94 min (CH_3CN/H_2O 7:3); UV (MeOH) λ_{max} 243 nm (ϵ 31 270); IR 1725, 1685, 1407, 1227 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.91−1.98 (m, 1H), 2.30−2.56 (m, 3H), 3.56 (t, 2H), 3.90 (s, 3H), 3.91 (s, 3H), 4.19−4.26 (m, 1H), 4.76 (t, 1H); ^{13}C NMR (DMSO-d_6) d 22.7, 29.8, 53.26, 61.9, 63.3, 89.3, 97.8, 102.5, 143.7, 147.9, 148.1, 167.9, 173.3; MS: m/z 686 (MH^+); Anal. Calcd for $C_{15}H_{14}I_3NO_6$: C, 26.30; H, 2.06; I, 55.58; N, 2.05. Found: C, 26.73; H, 1.85; I, 55.93; N, 2.04.

5-[2-(Hydroxymethyl)-5-oxo-1-pyrrolidinyl]-[*N*,*N*′-bis-(2,3- dihydroxypropyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (17d). Starting from **14b** (5.06 g, 5 mmol), **17d** was obtained as a white amorphous solid (3.25 g, 83%); mp 273−278 °C; TLC R_f 0.3 ($CHCl_3$/MeOH 7:3); HPLC t_R 9.7 min (column, aminopropyl; solvent, CH_3CN/H_2O 8:2); flow rate 1 mL/ min); UV(MeOH) λ_{max} 244 nm (ϵ 28 546); IR 3410, 1647, 1560, 1411 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.90−2.20 (m, 1H), 2.20−2.60 (m, 3H), 3.0−3.85 (m, 12H), 4.05−4.20 (bs, 1H), 3.35−4.90 (m, 5H, exchangeable), 7.60−8.60 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 23.3, 23.4, 29.7, 42.5, 42.6, 61.6, 61.8, 62.5, 63.9, 69.9, 91.4, 97.1, 97.4, 101.1, 101.5, 143.5, 150.5, 150.6, 169.5, 172.9, 173.0; MS m/z 804 (MH^+), 703, 678. Anal. Calcd for $C_{19}H_{24}I_3N_3O_8 \cdot 2.02H_2O$: C, 27.18; H, 3.01; I, 45.35; N, 5.01. Found: C, 27.44; H, 3.24; I, 45.17; N, 4.73, H_2O, 4.33.

***N*,*N*′-Bis[2-Hydroxy-1-(hydroxymethyl)ethyl]-5-[2-(hydroxymethyl)-5-oxo-1-pyrrolidinyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (17e).** Starting from **14c** (8.4 g, 8.3 mmol), **17e** was obtained as an amorphous white solid (5.88 g, 88%): mp 240−246 °C; UV (MeOH) λ_{max} 243.8 nm (ϵ 28 546); IR 3420, 1645, 1558, 1410 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.05 (m, 1H) 2.20−2.60 (m, 3H), 3.30−3.90 (m, 12H), 4.13 (m, 1H); 4.40−4.95 (m, 5H), 7.50−7.85 (m, 0.4H), 8.32 (m, 1.6 H); ^{13}C NMR (DMSO-d_6) δ 23.2,23.4, 29.7, 52.7, 53.1, 58.9, 58.98, 59.1, 61.4, 61.7, 62.5, 91.3, 91.4, 96.8, 97.2, 100.9, 101.3, 143.2, 143.3, 150.2, 150.3, 168.8, 168.8, 168.9, 168.9, 172.8, 172.1; MS m/z 804 (MH^+), 713, 678. Anal. Calcd for $C_{19}H_{24}I_3N_3O_8 \cdot 0.65H_2O$: C, 28.01; H, 3.13; N, 5.16; I, 46.73. Found: C, 27.99; H, 3.24; N, 4.97; I, 47.05; H_2O, 1.43.

5-[3-(Hydroxymethyl)-5-oxo-4-morpholinyl]-2,4,6-triiodo-1,3-benzenedicarboxylic Acid, Dimethyl Ester (18a). Starting from **15a** (430 mg, 0.58 mmol), **18a** was obtained as a white microcrystalline solid (375 mg, 93%), after crystallization from EtOAc: mp 225−226 °C; TLC R_f 0.28 (EtOAc/hexane 2:3); HPLC t_R 4.0 min (CH_3CN/H_2O 7:3); UV (MeOH) λ_{max} 243 nm (ϵ 33 525); IR 1734, 1653, 1523, 1435, 1418, 1330, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.76 (m, 2H); 3.98 (s, 3H), 3.99 (s, 3H), 4.04−4.10 (m, 2H), 4.34 (dd, 1H, J_{gem} = 13.5 Hz), 4.73 (ABq, 2H, J_{AB} = 17.3 Hz); ^{13}C NMR (DMSO-d_6) δ 53.4, 59.4, 60.5, 64.0, 89.7, 98.4, 102.3, 145.6, 148.1, 148.6, 165.7, 167.9; MS m/z 702 (MH^+) 670, 574. Anal. Calcd for $C_{15}H_{14}NI_3O_7 \cdot 0.24H_2O$: C, 25.54; H, 2.07; I, 53.98; N, 1.99. Found: C, 25.79; H, 1.72; I, 53.96; N, 2.05; H_2O, 0.61.

***N*,*N*′-Bis(2,3-dihydroxypropyl)-5-[3-(hydroxymethyl)-5-oxo-4- morpholinyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (18d).** Starting from **15b** (5.15 g, 5 mmol), **18d** was obtained as a white amorphous solid (3.25 g, 80%); mp 227−230 °C; TLC R_f 0.31 ($CHCl_3$/MeOH 4:1); HPLC t_R 9.2 min (column, aminopropyl (4.6 mm × 25 cm); solvent, CH_3CN/H_2O 8:2); flow, 1 mL/min); UV (CH_3CN) λ_{max} 242 nm (ϵ 30 100); IR 3328, 1644, 1553, 1441, 1420, 1341, 1269 cm^{-1}; ^1H-NMR-(DMSO-d_6) δ 3.16, 3.27 (m, 2H), 3.37−3.48 (bp, 6H), 3.6−4.0 (m, 5H), 4.51 (OH), 4.71 (OH), 5.11 (OH), 8.56 (NH); ^{13}C NMR (DMSO-d_6) δ 42.6, 42.7, 58.8, 60.2, 63.8, 64.0, 68.4, 70.0, 70.1, 91.8, 97.6, 98.0, 101.0, 101.4, 145.0, 145.1, 150.6, 151.1, 165.5, 169.6; MS m/z 820 (MH^+), 729, 694, 662, 603, 568; Anal. Calcd for $C_{19}H_{24}I_3N_3O_9 \cdot 1.03H_2O$: C, 27.24; H, 3.14; I, 45.45; N, 5.02. Found: C, 27.58; H, 3.25; I, 45.60; N, 4.93, H_2O, 2.21.

***N*,*N*′-Bis[2-Hydroxy-1-(hydroxymethyl)ethyl]-5-[3-(hydroxymethyl)-5-oxo-4-morpholinyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (18e).** Starting from **15c** (1 g, 1 mmol), **18e** was obtained as a white solid (0.65 g, 79%): mp > 250 °C; TLC R_f 0.38 ($CHCl_3$/MeOH 5:1); HPLC t_R 5.4 min (column, aminopropyl; solvent, CH_3CN/H_2O (7:3); flow, 1 mL/min); UV (CH_3CN) λ_{max} 242 nm (ϵ 29 700); IR 1647, 1549, 1419, 1341, 1271 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.58 (bd, 8H), 3.83 (m, 2H), 4.23 (ABq, 2H, J_{AB} = 16.7 Hz, Δ_{AB} = 29 Hz), 4.53 (m, 2H), 5.02 (t, OH), 5.1 (t, OH), 7.4−7.9 (4d, 2H); ^{13}C NMR (DMSO-d_6) δ 52.9, 53.3, 59.1, 59.3, 60.2, 60.3, 63.9, 68.1, 91.5, 97.5, 101.5, 144.7, 150.5, 151.0, 165.5, 169; MS m/z 820 (MH^+), 729, 694. Anal. Calcd for $C_{19}H_{24}I_3N_3O_9 \cdot 0.35H_2O$: C, 27.64; H, 3.02; I, 46.12; N, 5.09. Found: C,27.82; H,2.90; I,45.83; N,5.01; H_2O, O.77.

Dimethyl 5-[(2-Hydroxyacetyl)amino]-2,4,6-triiodo-1,3-benzenedicarboxylate (20). Following the general procedure described for acylation, treatment of the amine **3a** (4.7 g, 8 mmol) with (acetyloxy)acetyl chloride (2.1 g, 15 mmol) in DMA (25 mL) for 15 h, followed by crystallization of the crude from EtOAc, gave the corresponding (acetyloxy)anilide (4.95 g, 90%). Deacetylation of this product (687 mg, 1 mmol), by treatment with NaOMe (50 mg) in MeOH (10 mL) for 1 h, and further crystallization from EtOAc/hexane furnished the hydroxyacetanilide **20** as a white crystalline solid (580 mg, 90%); HPLC t_R 4 min (column, C8 reversed phase; solvent, CH_3CN/H_2O 6:4; Flow, 1 mL/min); ^1H NMR (DMSO-d_6) δ 3.98 (s, 6H), 4.20 (s, 2H); ^{13}C NMR (DMSO-d_6) δ 53.3, 61.9, 88.2, 100.1, 143.9, 147.5, 168.1, 170.9; MS m/z 646 (MH^+). Anal. Calcd for $C_{12}H_{10}I_3NO_6$: C, 22.33; H, 1.55; I, 59.07; N, 2.17. Found: C, 22.51; H, 1.32; I, 58.81; N, 2.25.

5-[(4,5-Dihydroxy-1-oxopentyl)amino]-*N,N'*-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide (22). To a solution of **6b** (2.86 g, 3 mmol) in acetone (10 mL) were added $Et_4NOAc{\cdot}4H_2O$ (196 mg, 0.75 mmol) and 90% t-BuOOH (0.54 mL, 5.4 mmol). The resulting solution was cooled in an ice bath, and the OsO_4 reagent (0.30 mL, made from 1 g of OsO_4, 199 mL of t-BuOH, and 1 mL of 90% t-BuOOH) was added. The reaction mixture was allowed to warm to room temperature and then stirred overnight. A freshly prepared 10% $NaHSO_3$ solution was added until the Quantofix peroxide paper test was negative. Solvents were removed and the residue was dissolved in 1:1 EtOAc/THF (10 mL). The solution was washed with brine (10 mL), dried, and the solvent removed. Purification of the residue by silica gel column chromatography using 3% MeOH in $CHCl_3$ afforded **21** as an off white amorphous solid (180 mg, 60.8%): ^1H NMR ($CDCl_3$) δ 2.05 (m, 2H), 2.10 (s, 12H), 2.58 (m, 2H), 3.55 (m, 4H), 3.76 (m, 4H), 4.28 (m, 2H), 5.28 (m, 3H); MS m/z 989.9 (MH^+).

Deacetylation of **21** (140 mg, 0.14 mmol) by treatment with NaOMe (0.14 mmol) in MeOH (5 mL) as described in the general procedure for deacetylation given above, afforded pure **22** as a white glassy solid (65 mg, yield 56%); HPLC t_R 26.1 min (column: aminopropyl 4.6 mm × 25 cm; solvent, 85% CH_3CN/H_2O flow rate 1.0 mL/min); ^1H NMR (D_2O) δ 1.68–1.95 (m, 2H); 2.52 (m, 2H); 3.23–3.95 (m, 13H); ^{13}C NMR (D_2O) δ 29.2, 33.5, 43.8, 65.05, 71.5, 67.0, 72.5, 90.8, 99.8, 144.1, 150.9, 173.7, 177.0; MS m/z: 821.8 (MH^+). Anal. Calcd for $C_{19}H_{26}I_3N_3O_9{\cdot}0.99H_2O$: C, 27.20; H,3.36; N. 5.01; I 45.38; O, 19.05. Found: C, 27.41; H, 3.11; N, 4.80; I, 45.58.

Hydrolytic Stability Studies. The hydrolytic stability studies were carried out with aqueous solutions of **16d**, **17d**, and **18d** at pH values 2, 6, and 12. Solutions of **16d**, **17d**, and **18d** (0.01 M) were prepared in deionized water (pH 6). Aqueous solutions of the iminofuran **16d** (0.01 M) were also prepared in 10 mM HCl (pH 2), deionized water (pH 6), or 10 mM NaOH (pH 12). The solutions were heated in sealed tubes at 85 or 100 °C for various time periods and then analyzed by HPLC using an aminopropyl silica column (4.6 mm × 25 cm) (solvent, CH_3CN/H_2O 75:25; flow, 1 mL/min). The decomposition products were quantified by the relative intensity of HPLC chromatographic peaks and identified by coinjection with authentic samples.

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