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# Smiles Rearrangement as a Tool for the Preparation of 5-[(2-Hydroxyacyl)amino]-2,4,6-triiodo-1,3-benzenedicarboxamides: Main Pathway and Side Reactions.

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***Abstract***: In the preparation of 5-[(2-hydroxyacyl)amino]-2,4,6-triiodo-1,3-benzenedicarboxamides **1a-h** from **2a-h** two conditions using stoichiometric amounts of base (method A - aq NaOH at 50 °C; method B - MeONa in DMF at r. t.) were used. Yields are good to excellent provided that the right conditions are chosen. Primary amides **2a,b** give **1a,b** with method B only, whereas with method A extensive hydrolysis of the $CONH_2$ moiety is observed. *N*-Methyl derivatives **2c,d** afford **1c,d** with either method. However, with method B long reaction times lead to the formation of large amounts of benzoxazinones, **4c,d**. Under the same conditions, the pattern of side products which are formed from *N*-(hydroxyalkyl)phenoxyacetamides **2e-g** is furtherly complicated by: *i*) intramolecular cyclizations leading to bicyclic (**7f,g**) and tricyclic structures (**5**) *ii*) *N*-deacylation; *iii*) double Smiles rearrangement reactions. © 1997 Elsevier Science Ltd.

## INTRODUCTION

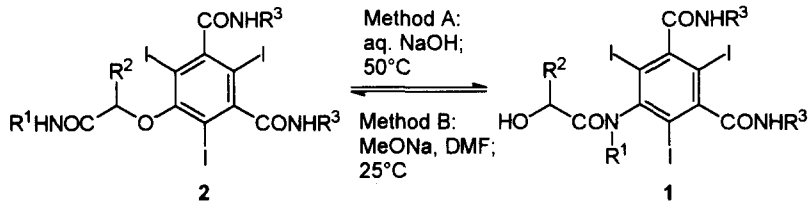
In 1995 the worldwide market for iodinated X-ray contrast agents was estimated to be worth more than $ 3 billion,[1] with non ionic contrast agents[2] such as Iopamidol,[3] **1a**, occupying a prevalent position. This compound is industrially prepared by acylation of a 5-amino-2,4,6-triiodo-1,3-benzenedicarboxylic acid derivative with (*S*)-2-acetoxypropanoyl chloride. A similar synthetic route was used to synthetise a new non ionic contrast agent, namely Iomeprol, **1c**.[4] During the preclinical studies necessary for its development it was unexpectedly found[5] that this compound, under conditions of accelerated degradation in alkaline solution, forms an equilibrium mixture containing **1c** and a small amount (2.4%) of **2c**. This latter compound is formed *via* Smiles rearrangement.[6] This finding was exploited to devise a new synthetic pathway for **1c** starting from **2c**, which is easily prepared from *N,N'*-bis(2,3-dihydroxypropyl)-5-hydroxy-2,4,6-triiodo-1,3-benzenedicarboxamide. This route is currently used for the industrial preparation of **1c**.[7] Preliminary results were reported on the use of Smiles rearrangement conditions for the preparation of 5-[(2-hydroxyacyl)amino]-2,4,6-triiodo-1,3-benzenedicarboxamides other than **1c**.[8] Here we describe a detailed investigation on the use of different basic conditions (aq NaOH *vs* MeONa in DMF) with a variety of substrates, **2a-h**, to achieve the conversion **2** → **1** (*i. e.* **2e** leads to **1e**, Ioversol, which is another commercially available contrast agent). Emphasis is placed on the identification of side-products which are formed due to the reaction conditions and/or to the structural features of the substrates **2**.

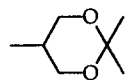
Base-promoted rearrangement of phenoxyacetamides to *N*-(hydroxyacetyl)anilines has been reported previously.[9] In some cases the latter compounds deacylate under the rearrangement conditions to give the corresponding anilines directly.[9c-e] The issue of electronic effects of substituents on the aromatic ring in Smiles rearrangement reactions has been raised in several papers.[6] Although some authors stressed the importance of the presence of electronwithdrawing groups in *ortho* and/or *para* positions of the aromatic ring, Smiles rearrangements on aromatic substrates deactivated towards nucleophilic substitutions have also been reported.[6]

## RESULTS AND DISCUSSION

Smiles rearrangement reactions are usually promoted by bases under different experimental conditions which range from aqueous bases[10] to alkali hydrides in suitable solvents.[9a-c,e] The choice is usually based on evaluation of: *i*) the basicity/nucleophilicity balance of the group which attacks the aromatic ring to form the Jackson-Meisenheimer intermediate;[11] *ii*) the solubilities of educt and product. Accordingly, for substrates **2a-h** we selected two experimental conditions: *i*) aq NaOH (1 mol equiv) at 50°C - method A; *ii*) sodium methoxide (1 mol equiv) in DMF at 25°C - method B.[12] The results of reactions performed on substrates **2a-h** are reported in Table 1.

**Table 1.** Smiles rearrangement performed on substrate **2a-h**



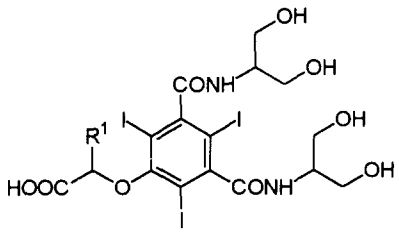

| Entry (2 → 1) | $R^1$ | $R^2$ | $R^3$ | Method A | | Method B | |
|---|---|---|---|---|---|---|---|
| | | | | time (h) | 1, yield[a] (%) | time (h) | 1, yield[a] (%) |
| **a**[b] | H | Me | $CH(CH_2OH)_2$ | 19 | 17.9[c] | 0.75 | 99.0 |
| **b** | H | H | $CH(CH_2OH)_2$ | 28 | 1.4[d] | 1 | 95.5 |
| **c** | Me | H | $CH_2CHOHCH_2OH$ | 24 | 91.1 | 0.1 | 94.2[e] |
| **d**[b] | Me | Me | $CH(CH_2OH)_2$ | 7 | 97.8 | 0.1 | 72.0[f] |
| **e** | $CH_2CH_2OH$ | H | $CH_2CHOHCH_2OH$ | 6.5 | 70.1[g] | 0.1 | 83.3[h,i] |
| **f** | $CH_2CHOHCH_2OH$ | H | $CH_2CHOHCH_2OH$ | 5 | 56.4[j] | 0.1 | 64.9[k,l] |
| **g**[m] | $CH(CH_2OH)_2$ | H | $CH(CH_2OH)_2$ | 28 | -[n] | 0.4 | -[o,p] |
| **h** |  | H | $CH(CH_2OH)_2$ | 1.5 | 9.1[q] | 0.1 | 10.9[r,s] |

[a] Determined by HPLC using as standards authentic samples of the products isolated in previous runs. [b] The (*S*) enantiomer was used. [c] **2a** (43.0%) and **3a** (39.1%). [d] **2b** (8.3%) and **3b** (89.6%). [e] After 2.5 h: **1c** (77.8%) and **4c** (15.3%). [f] **4d** (23.2%). [g] **2e** (24.9%). [h] **2e** (9.5%). [i] After 5 h: **1e** (38.5%), **2e** (15.0%), **5** (18.4%), and **6e** (3.4%). [j] **2f** (40.9%). [k] **2f** (29.5%). [l] After 3 h: **1f** (25.6%), **2f** (26.6%) and **8f** (21.8%). [m] With neither method **1g** was formed. [n] **2g** (73.9%) and **3b** (21.7%). [o] **2g** (51.8%), **6g** (21.5%), **7** (5.7%) and **8g** (14.5%). [p] After 3 h: **2g** (4.0%), **6g** (43.5%), **7** (12.5%) and **8g** (30.0%). [q] **2h** (90.1%). [r] **2g** (85.4%). [s] After 2.5 h: **1h** (9.0%), **2h** (78.9%) and **4h** (5.9%).

Substrates **2** are converted, with method A in few hours and with method B in few minutes, into the **2** ↔ **1** equilibrium mixture whose composition is substrate and solvent dependent.[13] However, with either experimental condition the occurrence of side reactions may become relevant or even predominant over the rearrangement reaction and strongly depends on the nature of the substituent on the phenoxyacetamide nitrogen atom.

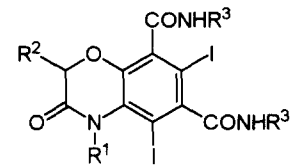
*Primary phenoxyacetamides:* with **2a,b**, whilst method B affords **1a,b** in excellent yields, method A leads to almost complete hydrolysis of the $CONH_2$ group yielding the corresponding acids **3a,b**.

*N-Methylphenoxyacetamides:* with **2c,d** both methods give **1c,d** in very good yields. However, prolonged reaction times with method B lead to noticeable amounts of benzoxazinones **4c,d** which derive from intramolecular nucleophilic substitution of the hydroxyacyl group on one of the ortho iodine atoms. Formation of benzoxazinones in Smiles rearrangements had already been observed[9c,e] and is clearly favoured in DMF, a solvent in which the reactivity of the hydroxyacyl group of **1c,d** is strongly enhanced. It is worth noting that formation of such cyclized products is not observed with substrates **2a,b**. Indeed, in the rearranged products **1a,b** the anilidic NH is more acidic than the OH of the hydroxyacyl group and therefore is preferentially salified under the reaction conditions.



**3a** $R^1$ = Me

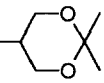
**3b** $R^1$ = H



**4c** $R^1$ = Me $R^2$ = H $R^3$ = $CH_2CHOHCH_2OH$

**4d** $R^1$ = $R^2$ = Me $R^3$ = $CH(CH_2OH)_2$

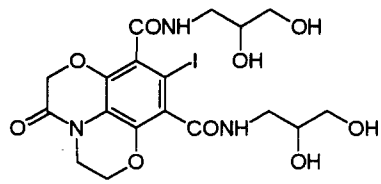
**4g** $R^1$ = $CH(CH_2OH)_2$ $R^2$ = H $R^3$ = $CH(CH_2OH)$

**4h** $R^1$ =  $R^2$ = H $R^3$ = $CH(CH_2OH)_2$

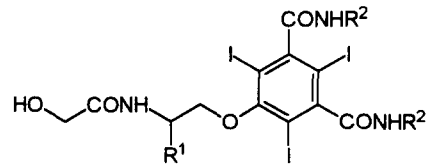
*N-(Hydroxyalkyl)phenoxyacetamides:* with **2e,f** method A affords, in 5 to 6.5 h, the equilibrium mixtures, which, compared to the mixtures obtained with substrates **2c,d**, contain a smaller amount of rearranged products. Use of method B with **2e,f** gives, in less than 10 min, **1e,f** in slightly better yields.[15] However, with longer reaction times the latter conditions lead to a pattern of products that derives from the reactivity of the hydroxy groups contained in both the acyl and the alkyl residues on the nitrogen atom in position 5 on the aromatic ring. In the case of substrate **2e**, after 5 h, the reaction mixture contains, apart from **1e**, tricycle **5**, which derives from a double intramolecular nucleophilic substitution on the rearranged derivative **1e**, and compound **6e**, which is formed *via* double Smiles rearrangement. Indeed, the first rearrangement of **2e** to **1e** is followed by a second rearrangement in which displacement *via* a Jackson-Meisenheimer complex of the amide moiety is promoted by nucleophilic attack of the OH group contained in the hydroxyethyl residue. To our knowledge this is the first reported example of a double Smiles rearrangement even though a similar pathway has been postulated to explain the migration of the aryl group along a chain of three nucleophilic centers in the case of picryl derivatives of 3-methylamino-1,2-propanediol.[16] In the case of compound **2f** long reaction times with method B lead to the formation of considerable amounts of **7f**, which derive from **1f**

through deacylation and intramolecular cyclization. Unlike the reaction on **2e**, with **2f** a tricyclic compound like **5** was not detected in appreciable amounts as a component of the reaction mixture.

Since the preparation of anilides **1** in which the nitrogen atom in position 5 is linked to a secondary carbon atom of an hydroxyalkyl group was still an unsolved synthetic problem, we approached the preparation of **1g** *via* Smiles rearrangement. Initially, phenoxyacetamide **2g** was allowed to react under both experimental conditions. Neither method A nor B led to the rearranged compound. Aqueous conditions gave, after long reaction times, only significant amounts of phenoxyacetic acid **3b**.[17] Reaction in DMF afforded a mixture of compounds whose main components were: ether **6g**, again resulting from a double Smiles rearrangement, aniline **8** and the corresponding cyclized product **7g**.

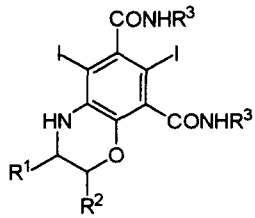


**5**



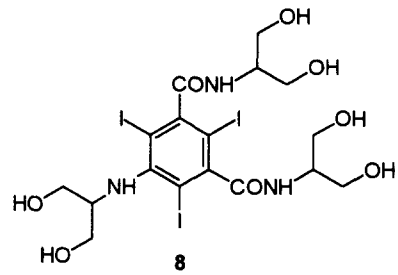
**6e** $R^1 = H$ $R^2 = CH_2CHOHCH_2OH$

**6g** $R^1 = CH_2OH$ $R^2 = CH(CH_2OH)_2$



**7f** $R^1 = H$ $R^2 = CH_2OH$ $R^3 = CH_2CHOHCH_2OH$

**7g** $R^1 = CH_2OH$ $R^2 = H$ $R^3 = CH(CH_2OH)_2$



**8**

In order to prevent intramolecular side reactions due to the presence of the OH groups in the dihydroxypropyl moiety, phenoxyacetamide **2h** was prepared and subjected to rearrangement. Under both reaction conditions the thermodynamic equilibrium is largely shifted towards the starting material, most probably as a consequence of the steric hindrance around the anilidic nitrogen in **1h**.[18] Compound **1h** was isolated from the rearrangement mixture and then deprotected by treatment with Amberlyst® 15 to afford **1g**. The impossibility of obtaining **1g** directly by Smiles rearrangement of **2g** was also confirmed by the evidence that **1g**, under aqueous basic conditions, immediately rearranges to **2g**.

In conclusion, we have shown that Smiles rearrangement allows easy access to derivatives **1**. However, attention has to be paid to the choice of the experimental conditions to avoid the formation of side products through different synthetic pathways.

## EXPERIMENTAL

All reagents and solvents, obtained from commercial sources, were used without further purification. MeONa was used as a 1 M solution obtained by dissolution of sodium in MeOH. Melting points were determined in open capillaries and are uncorrected. NMR spectra were recorded in $D_2O$ unless otherwise specified. $^1H$ NMR spectra are not reported since they are not useful for the assignment of the structures due to the broadness and extreme overlapping of the signals. The presence in solution of more then one atropoisomer, slowly interconverting on the NMR time scale, for 2,4,6-triiodo-1,3-benzenedicarboxamide derivatives is well established.[19] This explains the apparent complexity of the $^{13}C$ NMR spectra of some of the compounds here described. Numbering of the basic skeleton of the molecule and mention of neighbouring groups have been adopted to unambiguously identify carbon atom signals. FAB Mass spectra were recorded using glycerol as matrix. Elemental analyses were carried out at the Redox Laboratories (Cologno Monzese, Milano, Italy).

Compounds **2a-h** were prepared according to reported methodologies.[7a]

**Smiles Rearrangement Conditions (See Table 1). Method A:** 1 M aq NaOH (1 ml; 1 mmol) was added to a suspension of **2a-h** (1 mmol) in $H_2O$ (155 ml) and the mixture was stirred at 50 °C obtaining solution after 5-120 min. **Method B:** A 1 M solution of MeONa in MeOH (1 ml; 1 mmol) was quickly added to a 0.06 M solution of **2a-h** (16,6 ml; 1 mmol) in DMF and the resulting mixture was stirred at 25 °C.

**General Procedure for the Preparation of Compounds 1.** For preparative purposes methods A and B were applied on a suitable scale. After neutralisation (aq HCl) and evaporation under reduced pressure, the residues were desalted by ion exchange resins (Amberlite® C 20 MB and Duolite® A 30 B) then used for the isolation of the products according to the following methods: a) crystallisation; b) reverse phase preparative HPLC (Lichroprep® RP-8 or RP-18, 25-40 μm; $H_2O$/MeCN mixtures).

**(*S*)-*N,N'*-Bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[(2-hydroxy-1-oxopropyl)amino]-2,4,6-triiodo-1,3-benzenedicarboxamide (1a)** was prepared with method B followed by work-up a). Yield 89%: mp 285 °C (EtOH); $[\alpha]_D^{20}$ = - 3.20° (*c* 10, $H_2O$); $^{13}C$ NMR δ 22.2 ($CH_3$), 55.7 (NHCH), 62.5 ($CH_2OH$), 70.8 ($CH_3CH$), 91.7 (C2), 100.5 and 100.6 (C4 and C6), 144.8 (C5), 151.8 (C1 and C3), 174.4 and 174.5 (ArCO), 179.2 and 179.4 (CONHAr); ESI$^{(+)}$ MS *m/z* 778 (M + $H^+$) 800 (M + $Na^+$). Anal. Calcd for $C_{17}H_{22}I_3N_3O_8$: C, 26.28; H, 2.85; I, 48.99; N, 5.41. Found: C, 26.29; H, 2.88; I, 49.01; N, 5.39.

***N,N'*-Bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[(hydroxyacetyl)amino]-2,4,6-triiodo-1,3-benzenedicarboxamide (1b)** was prepared with method B followed by work-up a). Yield 83%: mp 300 °C (EtOH); $^{13}C$ NMR δ 55.9 (CH), 62.6 $(CH_2OH)_2$, 64.3 ($CH_2CO$), 91.6 (C2), 100.5 (C4 and C6), 145.0 (C5), 152.0 (C1 and C3), 174.6 (ArCO), 177.0 (CONHAr); ESI$^{(+)}$ MS *m/z* 764 (M + $H^+$) 786 (M + $Na^+$). Anal. Calcd for $C_{16}H_{20}I_3N_3O_8$: C, 25.18; H, 2.64; I, 49.89; N, 5.51. Found: C, 24.97; H, 2.70; I, 49.75; N, 5.49.

***N,N'*-Bis(2,3-dihydroxypropyl)-5-[(hydroxyacetyl)methylamino]-2,4,6-triiodo-1,3-benzenedicarboxamide (1c)** was prepared with method A followed by work-up a). Yield 81%: mp 300 °C (EtOH); $^{13}C$ NMR δ 37.2 ($CH_3$), 45.0 ($NHCH_2$), 63.9 ($COCH_2OH$), 66.5 ($CHOHCH_2OH$), 72.5 (CHOH), 93.4 (C2), 100.6 and 100.7 (C4 and C6), 148.1 (C5), 152.9 (C1 and C3), 174.3 and 174.4 (ArCO), 175.2 ($HOCH_2CO$);

ESI(+) MS *m/z* 778 (M + $H^+$) 800 (M + $Na^+$). Anal. Calcd for $C_{17}H_{22}I_3N_3O_8$: C, 26.28; H, 2.85; I, 48.99; N, 5.41. Found: C, 26.40; H, 3.01; I, 48.88; N, 5.39.

**(*S*)-*N,N'*-Bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[(2-hydroxy-1-oxopropyl)methylamino]-2,4,6-triiodo-1,3-benzenedicarboxamide (1d)** was prepared with method A followed by work-up a). Yield 91%: mp 298 °C (EtOH); $[\alpha]_D^{20}$ = + 12.77° (*c* 10, $H_2O$) $^{13}C$ NMR (DMSO-$d_6$) δ 21.2 ($CH_3CHOH$), 34.2 ($CH_3N$), 53.0 (NHCH), 59.2 ($CH_2OH$), 64.7 ($CH_3CH$), 91.9 (C2), 99.1 (C4 and C6), 146.7 (C5), 150.8 (C1 and C3), 169.0 (ArCO), 173.4 (CHCO); ESI(+) MS *m/z* 792 (M + $H^+$) 814 (M + $Na^+$). Anal. Calcd for $C_{18}H_{24}I_3N_3O_8$: C, 27.33; H, 3.06; I, 48.12; N, 5.31. Found: C, 27.66; H, 3.18; I, 47.97; N, 5.28.

***N,N'*-Bis(2,3-dihydroxypropyl)-5-[(hydroxyacetyl)(2-hydroxyethyl)amino]-2,4,6-triiodo-1,3-benzenedicarboxamide (1e)** was prepared with method B followed by work-up b). Yield 62%: mp 195 °C (EtOH); $^{13}C$ NMR δ 45.0 ($NHCH_2$), 53.9 ($CH_2N$), 61.6 ($CH_2CH_2OH$), 64.3 ($COCH_2OH$), 66.5 ($CHOHCH_2OH$), 72.5 (CHOH), 92.2 and 93.2 (C2), 101.5 and 102.5 (C4 and C6), 148.1 (C5), 152.6 and 153.0 (C1 and C3), 174.5 and 174.7 (ArCO), 175.8 and 176.5 ($HOCH_2CO$); ESI(+) MS *m/z* 830 (M + $Na^+$) 846 (M + $K^+$). Anal. Calcd for $C_{18}H_{24}I_3N_3O_9$: C, 26.79; H, 3.00; I, 47.17; N, 5.21. Found: C, 27.00; H, 3.22; I, 47.01; N, 5.15.

***N,N'*-Bis(2,3-dihydroxypropyl)-5-[(2,3-dihydroxypropyl)(hydroxyacetyl)amino]-2,4,6-triiodo-1,3-benzenedicarboxamide (1f)** was prepared with method B followed by work-up b). Yield 51%: mp 200 °C (EtOH); $^{13}C$ NMR (DMSO-$d_6$) δ 42.6 ($NHCH_2$), 53.8 ($CH_2N$), 61.9, 64.0 and 64.4 ($COCH_2OH$ and $CHOHCH_2OH$), 69.9 (CHOH), 91.9 (C2), 100.8 (C4 and C6), 145.7 (C5), 151.2 (C1 and C3), 169.6 (ArCO), 172.5 ($HOCH_2CO$); ESI(+) MS *m/z* 838 (M + $H^+$) 860 (M + $Na^+$). Anal. Calcd for $C_{19}H_{26}I_3N_3O_{10}$: C, 27.26; H, 3.13; I, 45.48; N, 5.02. Found: C, 27.47; H, 3.40; I, 45.27; N, 4.99.

***N,N'*-Bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[(hydroxyacetyl)[2-hydroxy-1-(hydroxymethyl)-ethyl]amino]-2,4,6-triiodo-1,3-benzenedicarboxamide (1g)** was prepared by acidic deprotection with Amberlyst® 15 resin of **1h** in water followed by work-up b). Yield 70%: mp 213 °C; $^{13}C$ NMR δ 55.9 (NHCH), 62.4 ($CHCH_2OH$), 64.8 ($COCH_2OH$), 65.0 (NCH), 93.1, 104.6 and 105.5 (C2, C4 and C6), 146.9 (C5), 152.6 (C1 and C3), 174.2 (ArCO), 176.2 ($HOCH_2CO$); ESI(+) MS *m/z* 838 (M + $H^+$) 860 (M + $Na^+$). Anal. Calcd for $C_{19}H_{26}I_3N_3O_{10}$: C, 27.26; H, 3.13; I, 45.48; N, 5.02. Found: C, 27.40; H, 3.21; I, 45.21; N, 4.95.

***N,N'*-Bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[(2,2-dimethyl-1,3-dioxan-5-yl)(hydroxyacetyl)-amino]-2,4,6-triiodo-1,3-benzenedicarboxamide (1h)** was prepared with method B followed by work-up b). Yield 2.9%: mp 128 °C; $^{13}C$ NMR δ 24.5 and 26.9 ($CH_3$), 54.6 ($CH_2O$), 55.7 (NHCH), 62.4 ($CHCH_2OH$), 63.1 (NCH), 64.4 ($COCH_2OH$), 93.6 (C2), 102.5 ($C(CH_3)_2$), 104.0 (C4 and C6), 146.1 (C5), 153.0 (C1 and C3), 174.1 (ArCO), 176.3 ($HOCH_2CO$); ESI(+) MS *m/z* 878 (M + $H^+$) 900 (M + $Na^+$). Anal. Calcd for $C_{22}H_{30}I_3N_3O_{10}$: C, 30.12; H, 3.45; I, 43.40; N, 4.79. Found: C, 29.89; H, 3.72; I, 43.19; N, 4.68.

**General Procedure for the Preparation of Compounds 4-8.** A 1 M solution of MeONa in MeOH (20-50 ml; 20-50 mmol) was added to a 0.06 M solution of **2a-h** (333 ml; 20 mmol) in DMF and the resulting

mixture was stirred at 25-50 °C. After evaporation under reduced pressure, the residue was purified according to the following methods: a) crystallisation; b) reverse phase preparative HPLC (Lichroprep® RP-8 or RP-18, 25-40 μm; $H_2O$/MeCN mixtures); c) silica gel chromatography (230-400 mesh).

***N,N'*-Bis(2,3-dihydroxypropyl)-3,4-dihydro-5,7-diiodo-4-methyl-3-oxo-2*H*-1,4-benzoxazine-6,8-dicarboxamide (4c)** was prepared from **2c** (MeONa 1.2 mol equiv; 25 °C; 3 h) and purified by work-up c) (eluent: 20 : 10 : 1 $CH_2Cl_2$/MeOH/2M $NH_3$ in MeOH) followed by work-up a). Yield 15%: mp 265 °C (MeOH); $^{13}C$ NMR δ 39.7 ($CH_3$), 44.9 and 45.1 ($NHCH_2$), 66.1 and 66.4 ($CH_2OH$), 71.7 (C2), 72.5 and 72.7 (CHOH), 86.5 and 87.8 (C5 and C7), 134.5 and 138.4 (C6 and C8), 146.5 and 148.8 (C4a and C8a), 171.3, 172.1 and 175.7 (ArCO and C3); FAB$^{(+)}$ MS *m/z* 650 (M + $H^+$) 524 (M + 2$H^+$ - $I^-$). Anal. Calcd for $C_{17}H_{21}I_2N_3O_8$: C, 31.45; H, 3.26; I, 39.10; N, 6.47. Found: C, 31.79; H, 3.51; I, 38.92; N, 6.29.

**(*S*)-3,4-Dihydro-*N,N'*-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5,7-diiodo-2,4-dimethyl-3-oxo-2*H*-1,4-benzoxazine-6,8-dicarboxamide (4d)** was prepared from **2d** (MeONa 1 mol equiv; 25 °C; 5 h) and purified by work-up c) (eluent: 30 : 10 : 1 $CH_2Cl_2$/MeOH/2M $NH_3$ in MeOH) followed by work-up a). Yield 18%: mp 265 °C (EtOH); $[\alpha]_D^{20}$ = + 8.50° (*c* 2, $H_2O$); $^{13}C$ NMR δ 17.1 ($CH_3CH$), 40.1 (NCH), 56.1 (NHCH), 63.0 ($CH_2OH$), 78.4 (C2), 86.5 and 87.9 (C5 and C7), 135.2 and 139.6 (C6 and C8), 146.6 and 148.2 (C4a and C8a), 171.2, 174.1 and 175.4 (ArCO and C3); FAB$^{(+)}$ MS *m/z* 664 (M + $H^+$) 686 (M + $Na^+$). Anal. Calcd for $C_{18}H_{23}I_2N_3O_8$: C, 32.60; H, 3.50; I, 38.27; N, 6.34. Found: C, 32.92; H, 3.79; I, 38.1; N, 6.12.

**3,4-Dihydro-*N,N'*-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5,7-diiodo-4-[2-hydroxy-1-(hydroxymethyl)ethyl]-3-oxo-2*H*-1,4-benzoxazine-6,8-dicarboxamide (4g)**; **1h** was reacted (MeONa 1.2 mol equiv; 25 °C; 15 h) to afford **4h** which was purified by work-up b) then deprotected with aq HCl to give **4g**. Yield 12%: mp 163 °C; $^{13}C$ NMR δ 55.8 and 55.9 (NHCH), 61.2 (NCH), 62.4 and 62.7 ($NHCH(CH_2OH)_2$), 63.9 ($NCH(CH_2OH)_2$), 71.2 (C2), 81.8 and 95.0 (C5 and C7), 140.9, 144.9, 146.2 and 147.2 (C6, C8, C4a and C8a), 171.8 (C3), 175.0 and 175.3 (ArCO); FAB$^{(+)}$ MS *m/z* 710 (M + $H^+$) 732 (M + $Na^+$). Anal. Calcd for $C_{19}H_{25}I_2N_3O_{10}$: C, 32.18; H, 3.55; I, 35.79; N, 5.92. Found: C, 32.50; H, 3.78; I, 35.41; N, 5.80.

***N,N'*-Bis(2,3-dihydroxypropyl)-2,3,5,6-tetrahydro-9-iodo-3-oxo-[1,4]oxazino[4,3,2-de]-1,4-benzoxazine-8,10-dicarboxamide (5)** was prepared from **2e** (MeONa 2 mol equiv; 50 °C; 3 h) and purified by work-up b). Yield 20%: mp 252 °C (EtOH); $^{13}C$ NMR (DMSO-$d_6$) δ 37.4 (C5), 42.5 ($NHCH_2$), 63.7 ($CH_2OH$), 64.5 and 67.0 (C2 and C6), 70.3 (CHOH), 85.9 (C9), 114.5 (C10b), 125.3 and 127.1 (C8 and C10), 140.5 and 141.1 (C7a and C10a), 161.3 (C3), 165.9 and 166.3 (ArCO); ESI$^{(+)}$ MS *m/z* 574 (M + $Na^+$) 1125 (2M + $Na^+$). Anal. Calcd for $C_{18}H_{22}IN_3O_9$: C, 39.22; H, 4.02; I, 23.02; N, 7.62. Found: C, 39.41; H, 4.18; I, 22.88; N, 7.49.

***N,N'*-Bis(2,3-dihydroxypropyl)-5-[2-[(hydroxyacetyl)amino]ethoxy]-2,4,6-triiodo-1,3-benzenedicarboxamide (6e)** was prepared from **2e** (MeONa 2 mol equiv; 50 °C; 3 h) and purified by work-up b) + c) (eluent: 6 : 3 : 1 $CHCl_3$/MeOH/25% $NH_4OH$) followed by work-up a). Yield 1.2%: mp 174 °C (MeOH); $^{13}C$ NMR (DMSO-$d_6$) δ 38.3 ($NHCH_2CH_2$), 42.5 ($NHCH_2CHOH$), 61.4 ($COCH_2OH$), 63.9 ($CHOHCH_2OH$), 70.0 (CHOH), 71.2 ($OCH_2$), 86.5 (C2), 90.7 (C4 and C6), 150.5 (C1 and C3), 157.4 (C5), 169.3 (ArCO),

172.1 ($HOCH_2CO$); $ESI^{(+)}$ MS *m/z* 808 ($M + H^+$) 830 ($M + Na^+$) 1636 ($2M + Na^+$). Anal. Calcd for $C_{18}H_{24}I_3N_3O_9$: C, 26.79; H, 3.00; I, 47.17; N, 5.21. Found: C, 26.87; H, 3.21; I, 47.02; N, 5.16.

***N,N'*-Bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[2-[(hydroxyacetyl)amino]-3-hydroxypropoxy]-2,4,6-triiodo-1,3-benzenedicarboxamide (6g)** was prepared from **2g** (MeONa 1.1 mol equiv; 25 °C; 16 h) and purified by work-up c) (eluent: 7 : 2 $CH_2Cl_2$/MeOH) followed by work-up b). Yield 8.8%: mp 148 °C; $^{13}C$ NMR δ 53.8 ($OCH_2CHNH$), 55.8 ($NHCH(CH_2OH)_2$), 62.6 ($NHCH(CH_2OH)_2$), 63.8 ($COCH_2OH$ and $CHCH_2OH$), 74.7 ($OCH_2$), 87.0 (C2), 92.9 (C4 and C6), 152.0 (C1 and C3), 160.6 (C5), 174.5 and 177.7 (ArCO and $COCH_2OH$); $ESI^{(+)}$ MS *m/z* 838 ($M + H^+$) 860 ($M + Na^+$). Anal. Calcd for $C_{19}H_{26}I_3N_3O_{10}$: C, 27.26; H, 3.13; I, 45.48; N, 5.02. Found: C, 27.20; H, 3.08; I, 45.31; N, 4.98.

***N,N'*-Bis(2,3-dihydroxypropyl)-3,4-dihydro-2-hydroxymethyl-5,7-diiodo-2*H*-1,4-benzoxazine-6,8-dicarboxamide (7f)** was prepared from **2f** (MeONa 2.5 mol equiv; 50 °C; 8 h) and purified by work-up b) + a). Yield 28%: mp 208 °C ($H_2O$); $^{13}C$ NMR (DMSO-$d_6$) δ 42.3 and 42.7 ($CH_2CHOH$ and C3), 60.7 ($CHCH_2OH$), 63.7 and 64.0 ($CHOHCH_2OH$), 70.1 and 70.4 (CHOH), 73.9 (C2), 74.8 and 82.2 (C5 and C7), 131.9, 135.0 and 138.5 (C4a, C6 and C8), 141.0, 166.8 and 170.4 (C8a and ArCO); $ESI^{(+)}$ MS *m/z* 674 ($M + Na^+$) 690 ($M + K^+$). Anal. Calcd for $C_{17}H_{23}I_2N_3O_8$: C, 31.36; H, 3.56; I, 38.98; N, 6.45. Found: C, 31.04; H, 3.69; I, 38.77; N, 6.23.

***N,N'*-Bis[2-hydroxy-1-(hydroxymethyl)ethyl]-3,4-dihydro-3-hydroxymethyl-5,7-diiodo-2*H*-1,4-benzoxazine-6,8-dicarboxamide (7g)** was prepared from **2g** (MeONa 1.1 mol equiv; 25 °C; 16 h) and purified by work-up c) (eluent: 7 : 2 $CH_2Cl_2$/MeOH) followed by work-up b). Yield 15%: mp 162 °C; $^{13}C$ NMR δ 53.8, 55.8 and 56.0 (C3 and $CH(CH_2OH)_2$), 62.7 and 62.9 ($NHCH(CH_2OH)_2$), 63.8 ($C3CH_2OH$), 68.5 (C2), 76.4 and 85.5 (C5 and C7), 133.3, 137.8 and 142.5 (C4a, C6, C8 and C8a), 172.6 and 175.8 (ArCO); $ESI^{(+)}$ MS *m/z* 652 ($M + H^+$) 674 ($M + Na^+$). Anal. Calcd for $C_{17}H_{23}I_2N_3O_8$: C, 31.36; H, 3.56; I, 38.98; N, 6.45. Found: C, 31.08; H, 3.41; I, 38.88; N, 6.32.

***N,N'*-Bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-2,4,6-triiodo-1,3-benzenedicarboxamide (8)** was prepared from **2g** (MeONa 1.1 mol equiv; 25 °C; 16 h) and purified by work-up c) (eluent: 7 : 2 $CH_2Cl_2$/MeOH) followed by work-up b). Yield 3.2%: mp 140 °C; $^{13}C$ NMR δ 55.7 (CONHCH), 62.5 ($CONHCH(CH_2OH)_2$), 62.9 (ArNHCH), 63.7 ($ArNHCH(CH_2OH)_2$), 82.6 (C2), 93.3 (C4 and C6), 151.6 and 153.1 (C1, C3 and C5), 175.1 and 175.3 (ArCO); $ESI^{(+)}$ MS *m/z* 780 ($M + H^+$) 802 ($M + Na^+$). Anal. Calcd for $C_{17}H_{24}I_3N_3O_8$: C, 26.21; H, 3.10; I, 48.87; N, 5.39. Found: C, 26.08; H, 3.27; I, 48.62; N, 5.17.

**General Procedure for the Preparation of Compounds 3a,b.** 1 M aq NaOH (100 ml; 100 mmol) was dropped, over 1 h, into a stirred suspension of the methyl ester of **3a** (or **3b**)[7a] (100 mmol) in $H_2O$ (200 ml) maintaining pH 10-10.5. After 1 h the solution was acidified to pH 1.8 with concd HCl then the crystalline solid was filtered, washed with $H_2O$ and dried to afford **3a** (or **3b**).

***(S)*-2-[3,5-Bis[[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]carbonyl]-2,4,6-triiodophenoxy]-propanoic acid (3a).** Yield 92%: mp 180 °C ($H_2O$); $[\alpha]_D^{20}$ = - 12.18° (*c* 15, 0.2 M NaOH); $^{13}C$ NMR

(DMSO-$d_6$) δ 18.1 and 18.3 ($CH_3$), 52.8 (NHCH), 59.2 ($CH_2OH$), 77.8 ($CH_3CH$), 86.0 (C2), 91.3 and 91.4 (C4 and C6), 150.2 (C1 and C3), 156.5 (C5), 169.0 (ArCO), 171.2 and 171.4 (COOH); $ESI^{(+)}$ MS *m/z* 779 ($M + H^+$) 801 ($M + Na^+$). Anal. Calcd for $C_{17}H_{21}I_3N_2O_9$: C, 26.24; H, 2.72; I, 48.93; N, 3.60. Found: C, 26.18; H, 2.81; I, 48.82; N, 3.51.

**[3,5-Bis[[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]carbonyl]-2,4,6-triiodophenoxy]acetic acid (3b).** Yield 96%: mp 243 °C ($H_2O$); $^{13}C$ NMR (DMSO-$d_6$) δ 52.9 (NHCH), 58.2 and 59.2 ($CH_2OH$), 68.1 ($CH_2CO$), 87.2 (C2), 90.4 (C4 and C6), 150.3 (C1 and C3), 156.7 (C5), 168.3 and 168.7 (ArCO and COOH); $ESI^{(+)}$ MS *m/z* 765 ($M + H^+$) 787 ($M + Na^+$). Anal. Calcd for $C_{16}H_{19}I_3N_2O_9$: C, 25.15; H, 2.51; I, 49.83; N, 3.67. Found: C, 25.00; H, 2.69; I, 49.61; N, 3.45.

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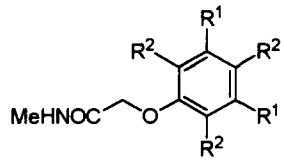
12. Although substoichiometric amounts of base can be used successfully for the rearrangement of secondary phenoxyacetamides, with primary phenoxyacetamides the use of 1 mol equiv of base is required because the rearranged anilides are salified.

13. For substrates **2** we separately analyzed the effect of the two carboxamide residues in *meta vs* that of the three iodine atoms in *ortho*, *ortho'* and *para* with respect to the rearrangement position. Compound **2i**,[14] which is devoid of the two carboxamide functions, gave the expected rearrangement product whereas **2j**,[14] lacking the three iodine atoms, either does not rearrange under basic conditions even at high temperature and under long reaction times (method B) or hydrolyses to the corresponding phenoxyacetic acid without rearrangement (method A).




**2i** $R^1 = H$ $R^2 = I$

**2j** $R^1 = CONHCH_2CHOHCH_2OH$ $R^2 = H$

14. Compounds **2i** and **2j** were prepared, according to a reported methodology,[7a] starting from 2,4,6-triiodophenol and *N,N'*-bis(2,3-dihydroxypropyl)-5-hydroxy-1,3-benzenedicarboxamide, respectively.
15. While with substrates **2a,b** (method B only) the equilibrium **2** ↔ **1** is fully shifted to the right due to salification of the anilidic NH, with substrates **2c-f** both methods lead to mixtures of **2** and **1** which mainly contain rearranged products **1c-f**. For each substrate the composition of such a mixture, being solvent dependent, is slightly different for the two methods. The higher content of rearranged product in the equilibrium mixtures derived from **2c,d**, compared to those derived from **2e,f**, could be related to the minor steric hindrance of the methyl group compared to that of the hydroxyalkyl groups.
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17. The presence of β- and γ-OH in *N*-alkyl residues of secondary and tertiary phenoxyacetamides noticeably accelerates the cleavage of the amide bond in water, even at neutral pH. See Anelli, P. L.; Brocchetta, M.; Canipari S.; Losi P.; Manfredi, G.; Tomba C.; Zecchi, G. *Gazz. Chim. Ital.* **1997**, *127*, in press.
18. As expected on the basis of the results described for **2c,d**, method B, after 2.5 h, led to the formation of benzoxazinone **4h**, which was characterized after deprotection to **4g**.
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