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Studies in the Design of X-Ray Contrast Agents. Synthesis, Hydrophobicity, and Solubility of Some Iodoresorcyl Bis(β-glucosides)

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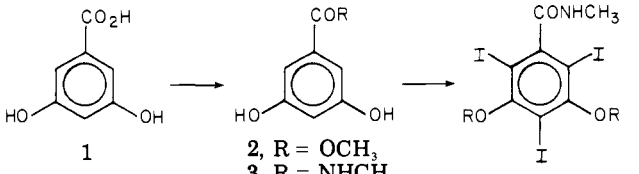
Two diiodo- and two triiodoresorcyl bis(β-glucosides) were prepared and their hydrophobicity (log $P_{octanol}$) and water solubility were compared to a triiodophenyl β-glucoside and several experimental nonionic, water-soluble, x-ray contrast agents. The data indicate steric overlap of the halogen substituents by the bulky hydrophilic O-β-glucosyl substituents; high water solubility is attained only at observed log $P_{octanol} \approx -1.5$ or lower. Of the new compounds, only 2,4,-6-triiodo-5-*N*-methylcarboxamidoresorcyl bis(β-glucoside) (**6**) was highly water soluble. At the physiological pH in dog's plasma in vitro, compound **6** rapidly hydrolyzed. Poorly water-soluble but more stable compounds of this series were not appreciably absorbed from dog's duodenum.

Previous work in this laboratory resulted in recent reports on the synthesis and toxicological evaluation of 2,4,6-triiodo-3-acetamido-5-*N*-methylcarboxamidophenyl β-D-glucoside (I)[1] and 2,4-diiodo-1,3,5-tri-*O*-glucosylbenzene (II).[2] Both compounds were tested as potential nonionic, water-soluble, x-ray contrast media (CM); the monoglucoside I and triglucoside II contained 51 and 29% iodine and had LD_{50} 25.5 and 34 g/kg body weight (mice), respectively. These low toxicity data justified synthesis of a bis(glucoside) derivative as a potentially useful radiographic water-soluble CM. In an effort to explore further the apparent detoxifying influence of the O-β-glucosyl moiety on CM, we measured octanol–H_2O partition coefficients (i.e., hydrophobicities, *P*) on I, II, and bis(β-glucosides) produced in this study. This approach seems especially appropriate to us since this laboratory has previously established a correlation between toxicity and the degree of interaction of proteins[3] with water-soluble CM.

Results and Discussion

A. Chemistry. In the course of this work, two new iodoresorcinals (**4** and **11**) were prepared as precursors to the bis(β-glucosides). Triiodoresorcinal **4** was prepared by esterification of α-resorcylic acid **1**, then amidation of ester **2**, and triiodination of amide **3** (Scheme I). The regiospecific 2,4-diiodination of resorcinol using the KIO_3–KI–HCl system[4] gave exclusively **11** with no NMR evidence for the 4,6 isomer **14** in crude product mixtures (Scheme II). The synthesis of both triiodoresorcinol (**8**) and 4,6-diiodoresorcinol (**14**)[5] was accomplished with ICl in aqueous HCl, the reagent of choice. Due to the instability of di- and triiodoresorcinols toward dilute aqueous hydroxide, conditions under which iodine is soon liberated, it was necessary to resort to the milder reaction conditions offered by the Ag_2O–quinoline medium for the reaction with α-acetobromoglucose, according to the procedure of Robertson and Waters.[6]

Scheme I

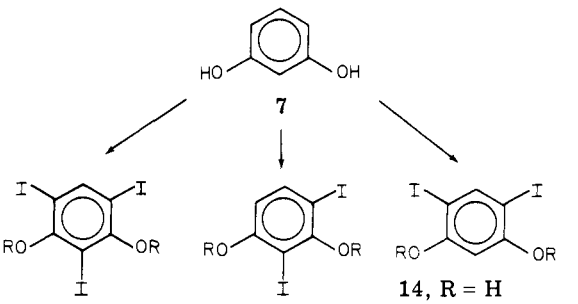


1

2, R = OCH_3
3, R = $NHCH_3$

4, R = H
5, R = Ac_4Glu
6, R = Glu

Scheme II



7

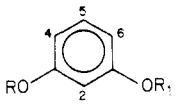
8, R = H
9, R = Ac_4Glu
10, R = Glu

11, R = H
12, R = Ac_4Glu
13, R = Glu

14, R = H
15, R = Ac_4Glu
16, R = Glu

Glucosidation of iodoresorcinols (**4**, **8**, **11**, and **14**) using 2 mol of α-acetobromoglucose and Ag_2O in quinoline with THF as diluent gave moderate to low yields (29–40%) of the corresponding octaacetyl bis(β-glucosides) (Table I). Application of this reaction to 2,4,6-triiodophenol (**17**) resulted in a 76% yield of the tetraacetylphenyl β-glucoside (**18**), a compound originally prepared[7] using aqueous hydroxide as the acid acceptor (Koenigs–Knorr reaction). However, reaction of triiodophloroglucinol (**21**)[4] with 3 mol of α-acetobromoglucose and Ag_2O in quinoline resulted in

Table I. Iodoresorcyl Glucosides and Precursors



No.	R	R_1	Substituents	Mp, °C (solvent)	Yield, %	Formula	Analyses
4	H	H	2,4,6-I_3, 5-$CONHCH_3$	212-213 (crude)[a]	80	$C_8H_6NO_3I_3$	N, I
5	Ac_4Glu[b]	$R_1 = R$	2,4,6-I_3, 5-$CONHCH_3$	145-155 (EtOAc-PE)	68	$C_{36}H_{42}NO_{21}I_3$	C, H, I
6	β-D-Glucosyl	$R_1 = R$	2,4,6-I_3, 5-$CONHCH_3$	165-175 dec (MeOH-EtOAc)	30	$C_{20}H_{26}NO_{13}I_3$	C, H, N, I
9	Ac_4Glu	$R_1 = R$	2,4,6-I_3	190-193 (EtOAc-PE)	40	$C_{34}H_{39}O_{20}I_3$	C, H, I
10	β-D-Glucosyl	$R_1 = R$	2,4,6-I_3	182 dec (MeOH-EtOH-Et_2O) (150, glass)	90	$C_{18}H_{23}O_{12}I_3$	H, I; C[c]
11	H	H	2,4-I_2	87-89 (CCl_4)[d]	41		
12	Ac_4Glu	$R_1 = R$	2,4-I_2	227-228 ($CHCl_3$-MeOH)	30	$C_{34}H_{40}O_{20}I_2$	C, H, I
13	β-D-Glucosyl	$R_1 = R$	2,4-I_2	195-200 (MeOH-EtOH-Et_2O)	70	$C_{18}H_{24}O_{12}I_2$	I
15	Ac_4Glu	$R_1 = R$	4,6-I_2	233-234.5 (EtOAc-PE)	29	$C_{34}H_{40}O_{20}I_2$	C, H, I
16	β-D-Glucosyl	$R_1 = R$	4,6-I_2	220-221 dec (MeOH-$CHCl_3$-PE)	53	$C_{18}H_{24}O_{12}I_2$	C, H, I
21	H	H	2,4,6-I_3, 5-OH	171-172 ($CHCl_3$)[e]	84		
22	Ac_4Glu	$R_1 = R$	2,4-I_2, 5-OAc_4Glu	155-157 (EtOH)[f]	3	$C_{48}H_{58}O_{30}I_2$	C, H; I[g]

[a] Crude product was washed with aqueous $Na_2S_2O_4$ and then water and then dried for analysis. [b] Ac_4Glu = 2,3,4,6-tetra-acetyl-β-D-glucosyl. [c] C: calcd, 26.62; found, 27.41. [d] Mp 87-89 °C (ref 4). [e] Mp 171-172 °C (ref 4). [f] Mp 155-157 °C (ref 8). [g] I: calcd, 18.54; found, 21.04.

Table II. Hydrophobicity (Log P) and Solubilities (S) of Iodoresorcyl Bis(β-glucosides) and Related Compounds

Compd	λ, nm[a]	Log P (butanol-H_2O)	Log P[b] (octanol-H_2O)	Log P_{calcd},[c] parent 6	$\Sigma\pi$	S, mol/l.
6	234	−0.54	−1.57		−0.54	∞
10	234	0.30	−0.74	0.30	0.73	4.93×10^{-3}
13	250	−0.29	−1.31	−1.65	0.62	1.20×10^{-2}
16	289	0.53	−0.25	−1.65	0.62	3.07×10^{-3}
20	233	1.34	1.68	2.31	3.34	1.67×10^{-5}
I	234	−0.26	−1.49	0.07	1.14	∞
II	220	−1.24		−4.26	−3.23	∞
III	240	−0.32	−1.89			∞

[a] Wavelengths at which partition coefficients (P) and solubility (S) were measured. [b] The experimental procedure (see Experimental Section) used for the generation of these data resulted in $P_{octanol} = 0.315$ for p-nitrophenyl β-D-glucoside in good agreement with the reported value (ref 12c), 0.366. [c] Calcd log $P_{octanol}$ values assuming additivity of Hansch $\pi\phi$ values: $-CONHCH_3$, −1.27; $-NHCOCH_3$, −0.97, as found in ref 13a; I, 1.35; $-C_6H_5$, 1.90, as found in ref 12b; glucose, −2.61, calculated from the data found in ref 12c.

intractable mixtures. Only a 3% yield (Table I) of the dodecaacetyl-2,4-diiodo-1,3,5-tri-*O*-glucosylbenzene[8] **22** was isolated after chromatography over neutral alumina followed by five recrystallizations from EtOH.

Deacetylation of the glucoside (**5**, **9**, **12**, **15**, and **18**) was routinely accomplished using cold methanolic ammonia[9] containing THF to solubilize the reactant.

B. Butanol–Water Partition Studies. More recent designs of nonionic CM have resulted in the synthesis of highly water-soluble sugar derivatives such as I and III (Metrizamide, i.e., 2-(3-acetamido-5-*N*-methylacetamido-2,4,6-triiodobenzamido)-2-deoxy-D-glucose].[10] The carbohydrate moiety in such molecules greatly decreases their overall hydrophobicity[1] making them the least toxic CM known. This design concept has also been verified in the very nontoxic triglucoside II.[2] In this work we have measured the 1-butanol–water[11] and the 1-octanol–water partition coefficients (P)[12] of glucosides of **6**, **10**, **13**, **16**, **19**, and I; compound II was too hydrophilic for measurement in the latter system. Observed log $P_{octanol}$ values are greatly more negative in every case than the calculated log P's obtained from $\Sigma\pi\phi$ according to Hansch $\pi\phi$ values (Table II). Considerably better agreement is obtained where bis(glucoside) **6** is used as parent compound and $\pi\phi$ substituent values are added or subtracted from the base value, −1.57. We interpret this to indicate that significant steric overlap of the hydrophobic iodoaryl ring occurs by the bulky and hydrophilic *O*-β-glucosyl substituents. A comparison of log $P_{octanol}$, −1.31 and −0.25 for diiodoresorcyl bis(β-glucosides) **13** (2,4-I_2) and **16** (4,6-I_2), respectively, suggests that an iodine substituent located between two carbohydrate moieties is more shielded (less hydrophobic) than an iodine which is ortho to only one. Thus, compound **13** is logically less hydrophobic than **16**. In this case, the solubilities of **13** and **16** parallel their log $P_{octanol}$ values (Table II, eq 2). A correlate of this physical evidence is the detoxifying effect of sugar moieties on CM verified in the unusually low intravenous toxicities of I[1] and II[2] and related compounds such as III.[10]

Equation 1 expresses the linear correlation between log

$$\log P_{butanol} = 0.526 \log P_{octanol} + 0.527 \quad (1)$$

$$n = 7; r = 0.972; s = 0.144$$

$P_{octanol}$ and log $P_{butanol}$ for *O*-β-glucosides **6**–**19**, I, and III; n is number of data points, r is the correlation coefficient, and s is the standard error of regression.

The success of such a correlation between partition coefficients is to be expected for reliable data.[13] Furthermore, the use of 1-butanol allows measurement of P

for more highly hydrophilic compounds such as II where the less polar 1-octanol cannot be employed (Table II). Thus, use of eq 1 allows calculation of log $P_{octanol}$, −3.4 for II.

Equation 2 expresses the linear correlation between

$$\log S = -0.982 \log P_{octanol} - 3.03 \quad (2)$$

$$n = 4; r = 0.988; s = 0.170$$

solubility (S) of O-β-glucosides **10**–**19** and their log $P_{octanol}$ values.

This relationship was confined to O-β-glucosides **10**, **13**, **16**, and **19** since all other compounds were too highly water soluble to be measured. This correlation may have a predictive value in future designs of highly water-soluble, nonionic CM. To achieve high solubility, it is apparently necessary to reach log $P_{octanol}$ values of about −1.5 or lower. Where high solubility has been achieved (**6**, I, II, and III) all three iodines are separated by a hydrophilic substituent of $\pi\phi$ equal to about −1.0 or less (Table II).

C. Biological Evaluation. An in vitro solution of compound **6** in plasma rapidly liberated free iodine (determined by starch iodide paper) indicating chemical instability of the β-glucoside bonds toward hydrolysis and subsequent iodine loss at pH >7. The determination of intravenous toxicity and excretion patterns in vivo was therefore deemed meaningless.

The more stable but poorly water-soluble compounds **10**, **13**, and **16** were tested as possible cholecystopaques by introducing them, as a slurry, into the duodenum of two anesthetised dogs. Subsequent iodine analysis[14] of samples of plasma, urine, and bile collected during 5 h pi showed that only traces of the compounds tested were absorbed from the gut and excreted into the bile.

Experimental Section

Partition Coefficients. The partition coefficients were measured by a modified Hansch procedure.[15] Typically a 1–3-mg sample was partitioned with 1–4 ml of alcohol and 1–4 ml of H_2O at 110 rpm on a shaker for 2 h; then the H_2O was drawn off and centrifuged for 0.5 h at 3000 rpm. All samples were run in triplicate and replicates agreed within ±4%. For this work (nonionic compounds, ≈10^{-3} M), the equation $P = (V_{H_2O}/V_{alcohol})[(C_{H_2Oi}/C_{H_2Of}) - 1]$ was used where the first factor is the ratio of water to alcohol volume used for partitioning of the substrate and the second factor contains the ratio of initial to final substrate concentrations in the water layer as determined by absorbance readings in the uv (Table II).

Solubilities were determined at 23 ± 2 °C by shaking an excess of substrate overnight in distilled water, filtering off the excess substrate, and then measuring the unknown uv absorbance either directly or after dilution. A standard curve (A vs. C_{H_2O}) of at least four points was used to determine the saturated solution concentration. Linear correlations were accomplished with a Data General, Nova 1220 computer.

Chemistry. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz. Unless otherwise noted, analyses indicated by symbols of the elements agree with calculated values within ±0.4% (C, H, N) and ±2.0% (I). Melting points were taken with a Thomas-Hoover apparatus using open capillaries and are uncorrected. Ir spectra (KBr) were taken on a Beckman Acculab 4 spectrophotometer. NMR spectra were recorded on a Varian EM-360 instrument using $CDCl_3$ and Me_4Si except where noted otherwise. Uv data were obtained on a Gilford 2400-S spectrophotometer equipped with digital readout. Evaporations were accomplished on a Büchi Rotovapor RE at ≤50 °C. Chemicals were purchased from the following sources: 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide from Sigma Chemical Co., St. Louis, Mo; ICl from Matheson Coleman and Bell. The aluminum oxide used was (basic or neutral, CAMAG) purchased from Ventron Corp., Alfa Products, Danvers, Mass. Compound **14**, i.e., 4,6-diiodoresorcinol, was prepared according to the procedure cited in ref 5.

Methyl α-Resorcylate (2). A concentrated solution of HCl in 50 ml of MeOH at reflux was used to esterify 15.4 g (0.10 mol) of **1** to obtain 14.6 g (87%) of tan solid **2**, mp 159–162 °C (lit.[16] 163–165 °C), which was used in a crude state.

5-*N*-Methylcarboxamidoresorcinol (3). A concentrated solution of H_2NCH_3 in 300 ml of MeOH at 60 °C (closed vessel) was used to amidate 40.0 g (0.24 mol) of **2** in 48 h. The product solution was evaporated to a syrup, dissolved in EtOH, and then decolorized by elution from a 6-in. column of neutral alumina. The EtOH fractions were combined and concentrated and EtOAc was added to turbidity to obtain, after several days, 32.0 g of tan solid **3**, mp 220–223 °C. Anal. ($C_8H_9NO_3$) C, H, N.

2,4,6-Triiodo-5-*N*-methylcarboxamidoresorcinol (4). To a solution of 3.0 g (0.018 mol) of **3** in 275 ml of H_2O was added at once, and with vigorous stirring, 112 ml of 0.8 N ICl in 1.6 N HCl (0.090 mol). Copious precipitate formed immediately. After stirring overnight at room temperature in a stoppered flask, the precipitate was collected by filtration, washed successively with H_2O, aqueous $Na_2S_2O_3$, and then H_2O, and dried in vacuo at 70 °C. Thus was obtained 8.5 g of pink solid **4**: mp 212–213 °C dec.

2,4,6-Triiodoresorcinol (8). Addition of 22.0 g (0.20 mol) of **7** to 875 ml of 0.8 M ICl in 1.6 M HCl (0.70 mol), vigorously stirred at 50 °C for 1 h, gave, after filtration, a dark crude solid which was dissolved in EtOAc, washed with aqueous $Na_2S_2O_3$, evaporated, and then recrystallized from boiling $CHCl_3$ (filtered while hot to clarify) to obtain 49.5 g (51%) of **8**: mp 154–157 °C (lit.[17] 154 °C); NMR (Me_2SO, D_2O, Me_4Si) δ 8.06 [s, 1 H, $C_6HI_3(OD)_2$].

2,4-Diiodoresorcinol (11). According to the procedure of Weitl[4] 11.0 g (0.100 mol) of **7** in 250 ml of H_2O containing 16.7 ml (0.20 mol) of concentrated HCl was iodinated by the addition (dropwise, 1 h) of 14.3 g (0.067 mol) of KIO_3 and 22.1 g (0.133 mol) of KI dissolved in 500 ml of H_2O. Work-up provided 20.3 g of white solid **11**: mp 87–89 °C (CCl_4).

2,4,6-Triiodophloroglucinol (21). Using the same procedure as for **11**, 10.0 g (0.62 mol) of phloroglucinol **20** (as dihydrate) and 15.1 ml of concentrated HCl (0.18 mol) slurried in 250 ml of H_2O were iodinated by addition of a solution of 13.2 g (0.062 mol) of KIO_3 and 20.5 g (0.123 mol) of KI in 400 ml of H_2O. Solid product was collected by filtration, washed with H_2O, and dried in vacuo at 75 °C to obtain 27.8 g of pink solid **21**: mp 171–172 °C dec ($CHCl_3$) (lit.[4] 171–172 °C dec).

2,3,4,6-Tetra-*O*-acetyl β-D-Glucosides (5, 9, 12, 15, 18, and 22). The general procedure[6] is illustrated by the following example. To 4.7 g (0.010 mol) of 2,4,6-triiodophenol (**17**) in a 100-ml flask (under Drierite tube) was added successively 4.9 g (0.012 mol) of 2,3,4,6-tetra-O-acetyl-α-D-bromoglucopyranose, 20 ml of THF, 20 ml of quinoline, and 2.8 g (0.012 mol) of Ag_2O. The initial heat evolution soon subsided and the resulting mixture was stirred (magnetic bar) or shaken 6 h. Next, the reaction mixture was diluted with about 50 ml of AcOH and filtered through a cake of Celite which was washed free of product with an additional ~100 ml of AcOH. The AcOH solution was drowned with 10 vol of H_2O to give a precipitate which was collected by filtration, washed with H_2O, dissolved in $CHCl_3$ (or EtOAc), dried with $MgSO_4$, filtered, and eluted from a 13 × 2 in. column of neutral alumina with $CHCl_3$ (or EtOAc). The column fractions were combined, evaporated, and recrystallized from boiling MeOH to give 6.1 g (76%) of white, crystalline 2,4,6-triiodophenyl-2,3,4,6-tetra-O-acetyl β-glucoside (**18**): mp 187–188 °C (lit.[7] 190–192 °C); ir 1740 cm^{-1} (CH_3CO–).

β-D-Glucosides (6, 10, 13, 16, and 19). The general procedure[9] is illustrated by the following example. To 5.9 g (0.074 mol) of **18** dissolved in 10 ml of THF was added 50 ml of 6 N NH_3–MeOH and the resulting solution stored at 0–5 °C overnight in a stoppered vessel. The solvent was then evaporated at room temperature and the residue showed complete absence of a 1740-cm^{-1} (CH_3CO–) band in the ir. Recrystallization from THF–Et_2O–PE gave 3.1 g (66%) of white powder, 2,4,6-triiodophenyl β-D-glucoside (**19**): mp 217–218 °C (lit.[7] 212–213 °C).

2,4,6-Triiodo-5-*N*-methylcarboxamidoresorcyl Bis(β-D-glucoside) (6). Following the general procedure for deacetylation, 38.5 g (31.9 mol) of **5** was treated with 200 ml of 6 N NH_3–MeOH to give an oil which could be purified either by several precipitations from MeOH with EtOAc or by column chromatography as follows. The deacetylation mixture was eluted from a 30 × 2 in. alumina column with EtOH–H_2O (6:4) to remove all phenolic

substances and then with MeOH to obtain bis(glucoside) 6: TLC [n-BuOH–AcOH–H_2O (4:1:1)] R_f 0.31 (on silica gel 60, E. Merck). Evaporation of bis(glucoside) fractions gave a syrup which was dissolved in MeOH and then precipitated with EtOAc to obtain 8.1 g of tan solid 6: mp 165–175 °C dec.

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Iodine-Containing Organic Carbonates as Investigative Radiopaque Compounds

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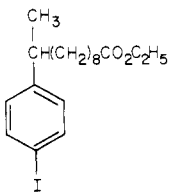
Carbonates containing an iodinated aromatic ring on one side of the carbonate linkage and an alkyl group on the other were prepared. The aromatic side consisted of *p*-iodophenyl, *p*-iodobenzyl, *m*-iodobenzyl, 3,5-diiodobenzyl, *m*-amino-2,4,6-triiodobenzyl, *m*-acetamido-2,4,6-triiodobenzyl, *p*-iodophenethyl, *p*-iodo-*sec*-phenethyl, 3-(*p*-iodophenyl)propyl, 3-(*p*-iodophenyl)butyl, 2-(*p*-iodobenzyl)butyl, and 2-(*p*-iodobenzyl)hexyl groups. The alkyl portion of the carbonates was derived from alkyl alcohols containing from two to ten carbon atoms. The approximate lethal dose of intraperitoneal injections ranged from less than 1 ml/kg to more than 15 ml/kg. An investigation into the use of these compounds as radiopaques for myelography, lymphography, bronchography, and salpingography is underway.

Positive contrast myelography is defined as the x-ray visualization of the subarachnoid space (SAS) after the injection of a radiopaque compound. Two approaches that have been used for myelography are (1) a water-insoluble oil, immiscible with cerebrospinal fluid (CSF),[1,2] and (2) a water-soluble compound, miscible with CSF and rapidly eliminated.[3-7] Oil myelography allows the physician sufficient time for examination and reexamination should it be necessary. The flow of the oil in the spinal column can be controlled through patient manipulation. The material can be positioned either anteriorly or posteriorly within the SAS while the patient is prone, thus allowing specific areas to be investigated. The high radiopaque density achieved with an oil column often provides a superior examination.[7]

Myelography in the United States is currently performed using ethyl iodophenylundecylate (1) (trademark, Pantopaque, by Lafayette Pharmacal Inc., Lafayette, Ind.). Since its development in the early 1940's it has dominated



1

the U.S. myelographic market.[1,8] Because 1 is only slowly absorbed by body processes, it is withdrawn by a syphonage technique at the conclusion of the examination. With meticulous attention to technique the withdrawal can be carried out painlessly with 99–100% of the medium removed all the time.[7,9] Over the years, this examination has had a high degree of patient safety.[9] Attempts have been made at preparing an oil that would be readily eliminated but to date 1 is the only product available for diagnostic use in the U.S.[4]

The water-soluble myelographic agent, sodium iodomethanesulfonate (**2**, Skiodan), has been used in the Scandanavian countries for more than 30 years. However,

ICH_2SO_3Na

2

a higher incidence of reaction and patient discomfort is seen.[3,4] Directions for use require the application of local anesthetics and precautions to avoid using the material above the lumbar region. From time to time various other ionic water-soluble radiopaques have been investigated.[10] The hypertonicity of these salt solutions is a major source for their toxic effects. Almen suggested in 1969 that the toxicity of water-soluble contrast agents could be reduced by synthesizing nonelectrolytic contrast agents in which the carboxyl group had been replaced by a nonelectrolytic hydrophilic radical.[11] In 1973 a new nonionic water-soluble radiopaque in which D-glucose amine was bonded to a triiodinated benzoic acid derivative was reported.[5] Evidence to date indicates that this compound, 2-[3-acet-