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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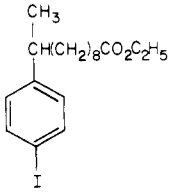
Carbonates containing an iodinated aromatic ring on one side of the carbonate linkage and an alkyl group on the other were prepared. The aromatic side consisted of *p*-iodophenyl, *p*-iodobenzyl, *m*-iodobenzyl, 3,5-diiodobenzyl, *m*-amino-2,4,6-triiodobenzyl, *m*-acetamido-2,4,6-triiodobenzyl, *p*-iodophenethyl, *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]

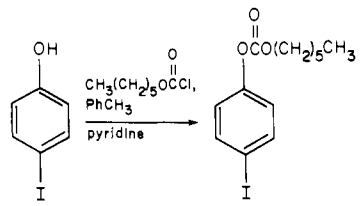
The water-soluble myelographic agent, sodium iodomethanesulfonate (2, Skiodan), has been used in the Scandanavian countries for more than 30 years. However,

ICH_2SO_3Na

2

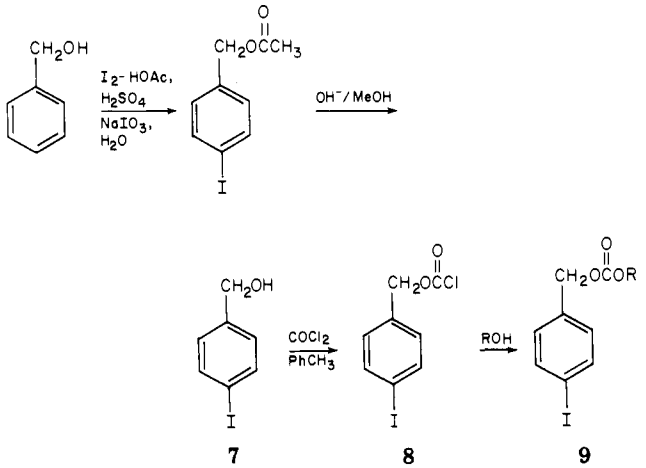
a higher incidence of reaction and patient discomfort is seen.[3,4] Directions for use require the application of local anesthetics and precautions to avoid using the material above the lumbar region. From time to time various other ionic water-soluble radiopaques have been investigated.[10] The hypertonicity 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-

Scheme I



4 5

Scheme II



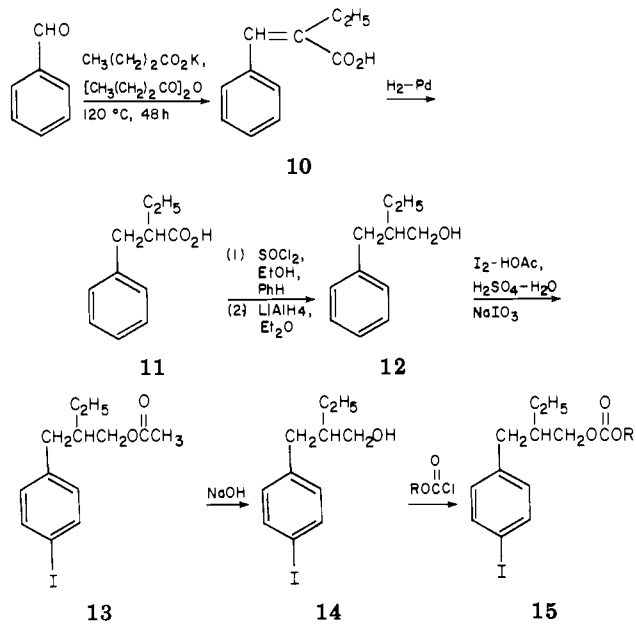
7 8 9

amido-5-(*N*-methylacetamido)-2,4,6-triiodobenzamido]-2-deoxy-D-glucose (3, Metrizamide), is an improvement over earlier ionic water-soluble formulas. However, because 3 is subject to hydrolysis it cannot be dispensed in solution and thus must be dissolved prior to injection. This, in addition to some side effects, lower radiographic density compared to 1, and limited examination time, due to rapid elimination, indicates that the ideal myelographic agent has not been found.[6,7] Recently two additional compounds formulated on the concept of bonding a sugar to an iodinated benzene ring have come to our attention.[12] From the preliminary testing the toxicity of these compounds appears to be on the same order as 3.

In efforts to prepare improved myelographic agents, several factors led to the investigation of water-insoluble oils rather than water-soluble compounds. The long dominance of the U.S. myelographic market by 1 has generated a large body of information on the interpretation of oil myelograms. This would be most valuable for new oily myelographic agents. The vast lymphatic network which communicates with the subarachnoid space provides a mode of elimination for certain oily compounds.[13] Finally, any myelographic agent must be nonirritating when in contact with the central nervous system and it was felt that this requirement could be more easily met through an oil rather than a water-soluble compound. Attempts at preparing such a compound led us to investigate iodinated organic carbonates.[14] Preliminary results with several of these compounds have been very encouraging.

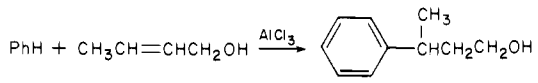
Chemistry. The carbonate linkage is formed by reacting a chloroformate with an alcohol.[15] Commercially available alkyl chloroformates, corresponding to desired carbonates, were allowed to react with iodinated aromatic alcohols as outlined in Scheme I. Alternatively, the chloroformate of either alcohol portion of the desired carbonate could be prepared by reacting the alcohol with phosgene in an inert solvent (Scheme II).[16] Iodination of the aromatic alcohols was achieved by treating with iodine in glacial acetic acid and sulfuric acid.[17] Under these conditions, the benzene ring is iodinated and the

Scheme III



10 11 12 13 14 15

Scheme IV



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alcohol is also converted to the acetate ester. The iodinated alcohol is then generated by hydrolysis of the ester (Scheme II).

3,5-Diiodobenzyl alcohol (16) was prepared by treating 2,3,5-triiodobenzoic acid with lithium aluminum hydride according to the procedure of Gaux and LeHanaff.[18] 3-Amino-2,4,6-triiodobenzyl alcohol (17) was prepared according to the procedure of Hebký and Karasek.[19] 3-Acetamido-2,4,6-triiodobenzyl alcohol (18) was prepared by treating 17 with acetic anhydride and a trace of acid.[19]

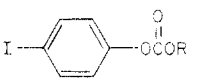
2-(*p*-Iodobenzyl)butanol (14) was prepared as outlined in Scheme III.[18] A Perkin condensation of benzaldehyde with potassium butyrate and butyric anhydride gave α-ethylcinnamic acid (10). Catalytic hydrogenation in 3% sodium hydroxide over Pd/C gave good yields of α-ethylhydrocinnamic acid (11). Treatment of the acid with thionyl chloride gave the acid chloride, which on combination with ethanol yields the ethyl ester. Reduction of the ester with lithium aluminum hydride in anhydrous ether gave 2-benzylbutanol (12, Scheme III). This alcohol was then iodinated in the standard manner (vide supra).

3-Benzylhexanol (47), used for the preparation of carbonate 48 in Table III, was also prepared by the Perkin condensation. The hexanoic anhydride and potassium hexanoate, necessary for the condensation, were prepared according to standard procedures.[18] The remaining steps for the preparation of 2-(*p*-iodobenzyl)hexanol (47) were the same as outlined for 14.

3-Phenylbutanol (19), required for the preparation of carbonates 41–43 in Table III, was prepared by a Friedel–Crafts condensation of benzene with crotyl alcohol (Scheme IV). 3-Phenylbutanol (19) was then converted to 3-*p*-iodophenylbutanol (20) using the procedure for the preparation of 14.

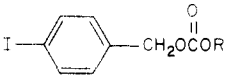
Toxicity. As an initial toxicity screen the compounds were injected intraperitoneally (ip) into mice using the technique of Kunz et al.[21] and the animals radiographed to confirm the location of the material. An approximate

Table I. *p*-Iodophenyl Carbonates



Compd	R	Bp (mm), °C	n^{25}D	Yield, %	*m/e* Calcd	*m/e* Found	ALD ip in mice, ml/kg
5	$-(CH_2)_5CH_3$	164 (0.5)	1.5340	75	348.0225	348.0210	4.5
21	$-(CH_2)_7CH_3$	154 (0.2)	1.5244	70	376.0538	376.0548	7

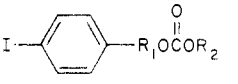
Table II. *p*-Iodobenzyl Carbonates



Compd	R	Bp (mm), °C	n^{25}D	Yield, %	*m/e* Calcd	*m/e* Found	ALD ip in mice, ml/kg
22	$-CH_2CH_3$	112 (0.4)	1.5587	65	*a*	*a*	1.7
23	$-CH_2CH(CH_3)_2$	125 (0.1)	1.5421	25	334.0068	334.0064	3
24	$-CH_2CH_2OCH_3$	165 (0.1)	1.5543	50	335.9861	335.9846	<1[b]
25	$-(CH_2)_4CH_3$	150 (0.3)	1.5439	30	348.0225	348.0231	3
26	$-(CH_2)_5CH_3$	171 (0.25)	1.5332	70	362.0381	362.0362	7
27	$-CH(C_2H_5)C_3H_7$	150 (0.3)	1.5348	58	362.0381	362.0359	3
28	$-CH(CH_3)CH_2CH(CH_3)_2$	140 (0.2)	1.5320	28	362.0381	362.0373	10.5
29	$-(CH_2)_7CH_3$	165 (0.1)	1.5299	50	390.0694	390.0673	>19[c]
30	$-CH_2CH(C_2H_5)C_4H_9$	185 (0.3)	1.5295	60	390.0694	390.0661	15
31	$-CH(CH_3)C_6H_{13}$	190 (0.6)	1.5259	24	390.0694	390.0665	>15[c]
32	$-CH(CH_3)CH_2CO_2C_2H_5$	190 (0.2)	1.5369	23	392.0123	392.0102	<3[b]
33	$-(CH_2)_9CH_3$	180 (0.1)	1.5224	80	418.1007	418.1002	>10.5[c]

[a] Anal. Calcd for $C_{10}H_{11}IO_3$: C, 39.22; H, 3.62; I, 41.48. Found: C, 39.24; H, 3.77; I, 41.49. [b] Lowest dose tested. [c] Highest dose tested.

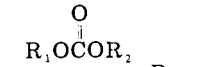
Table III. Dialkyl Carbonates



Compd	R_1	R_2	Bp (mm), °C	n^{25}D	Yield, %	*m/e* Calcd	*m/e* Found	ALD ip in mice, ml/kg
35	$-CH_2CH_2-$	$-CH_2CH_3$	141 (0.5)	1.5522	80	319.9911	319.9894	3
36	$-CH_2CH_2-$	$-(CH_2)_5CH_3$	165 (0.25)	1.5295	78	376.0538	376.0508	7
38	$-CH_2CH_2CH_2-$	$-CH_2CH_3$	173 (0.25)	1.5530	69	334.0068	334.0040	<3[b]
39	$-CH_2CH_2CH_2-$	$-(CH_2)_5CH_3$	167 (0.3)	1.5291	70	390.0694	390.0708	10.2
41	$-CH(CH_3)CH_2CH_2-$	$-CH_2CH_3$	147 (0.2)	1.5466	87	348.0224	348.0244	<2.2[b]
42	$-CH(CH_3)CH_2CH_2-$	$-CH(CH_3)_2$	145 (0.1)	1.5423	47	362.0381	362.0354	1.5
43	$-CH(CH_3)CH_2CH_2-$	$-(CH_2)_5CH_3$	173 (0.2)	1.5289	71	404.0850	404.0830	7
44	$-CH_2CH(C_2H_5)CH_2-$	$-CH_2CH_3$	147 (0.2)	1.5445	56	362.0381	362.0357	<2.2[b]
45	$-CH_2CH(C_2H_5)CH_2-$	$-C_4H_9$	148 (0.25)	1.5300	84	*a*	*a*	4.5
46	$-CH_2CH(C_2H_5)CH_2-$	$-(CH_2)_5CH_3$	168 (0.1)	1.5250	74	418.1007	418.0994	>15[c]
48	$-CH_2CH(C_4H_9)CH_2-$	$-(CH_2)_5CH_3$	185 (0.2)	1.5174	90	446.1320	446.1320	>15[c]

[a] Anal. Calcd for $C_{16}H_{23}IO_3$: C, 49.22; H, 5.94; I, 32.53. Found: C, 49.52; H, 6.13; I, 32.36. [b] Lowest dose tested. [c] Highest dose tested.

Table IV. Influence of Ring Substitution on Toxicity



Compd	R_1	R_2	Analyses	ALD
29	*p*-I-C_6H_4-CH_2-	C_8H_{17}	C, H, I	>19 ml/kg[a]
49	*m*-I-C_6H_4-CH_2-	C_8H_{17}	C, H, I	>17 ml/kg[a]
26	*p*-I-C_6H_4-CH_2-	C_6H_{13}	C, H, I	7 ml/kg
50	3,5-I_2-C_6H_3-CH_2-	C_6H_{13}	C, H, I	5 ml/kg
51	3-NH_2-2,4,6-I_3-C$_6$H-CH_2-	C_6H_{13}	C, H, I	>22 g/kg[a,b]
52	3-NHCOCH$_3$-2,4,6-I_3-C$_6$H-CH_2-	C_6H_{13}	C, H, I	>17 g/kg[a,b]

[a] Highest dose tested. [b] Administered in sesame oil.

lethal dose (ALD) was determined by injecting six animals with graduated doses, each dose 50% higher than the preceeding. Using this procedure all doses up to a certain level resulted in survival of the animals, while above this level all concentrations killed. On a series of 20 compounds, workers previously found the ALD obtained by this procedure agreed with the calculated LD_{50}'s within the limits of approximately ±30%.[22]

Tables I–IV summarize the data collected on the carbonates. As the carbon content of the alkyl portion of the carbonate increases, the ALD increased. This is exemplified by comparing **22**, **23**, **25**, **26**, and **29**. It is also seen when comparing **35** with **36**, **38** with **39**, **41** or **42** with **43**, and **44**, **45**, and **46**.

The effect of varying the carbon content between the iodinated phenyl ring and the carbonate linkage is less pronounced. Thus, while holding the alkyl side of the carbonate constant, the ALD goes from 4.5 ml/kg with *no* carbon between the benzene ring and the carbonate group to 7 ml/kg with *one* methylene (compare **5** with **26**). Variation from 1 to 4 carbon atoms between the ring and the carbonate group shows little change in ALD (compare **26**, **36**, **39**, and **43**). An increase in the ALD to above 15 ml/kg is seen, however, when a 2-ethylpropyl linkage is introduced between the ring and the carbonate group (note **46**).

No significant change was observed with the iodine in the meta rather than the para position (compare **29** with **49**). The toxicity remained essentially unchanged when the ring was substituted with iodine in the 3,5 position instead of the para position (compare **26** with **50**). However, **50** was less acceptable than **26** as a product because of its higher viscosity.

Previous workers have demonstrated that a *m*-amino group and a *m*-acetamido group both lower the toxicity of triiodinated radiopaque compounds.[23] Benzyl carbonates substituted in this manner gave solids as a final product. As expected, the toxicities of these materials, administered in sesame oil, were much less than the corresponding *p*-iodobenzyl derivatives (compare **26** with **51** and **52** in Table IV).

Follow-up radiographs on the animals surviving intraperitoneal injections routinely showed complete elimination of material in 1–2 weeks. Preliminary investigations into the use of these carbonates as myelographic, bronchographic, lymphographic, and salpingographic agents are underway. The results to date have been encouraging.

Experimental Section

p-Iodophenol was obtained from Eastman Kodak, Inc., and 2,3,5-triiodobenzoic acid and *m*-iodobenzyl alcohol were obtained from Aldrich Chemical Co.; all were used as received.

Melting points were determined on a Büchi capillary apparatus and are uncorrected. Ir spectra were recorded on a Beckman IR 33 spectrometer. NMR spectra were taken on a Varian EM 360 spectrometer using tetramethylsilane as the internal standard. Gas chromatograms were obtained on a Hewlett-Packard 5712A chromatograph equipped with a thermal conductivity detector using a 3% SE-30 column. Refractive indices were determined on a Bauch and Lomb refractometer. Mass spectra were obtained on a CEC 21-110B double-focusing mass spectrometer with an accelerating potential of 7.5 kV, nominal; an emission current of 100 μA, regulated; an ionizing voltage of 70 eV; a reservoir temperature of 200 °C; a source temperature of 175–200 °C; and a nominal mass resolution of 1/15 000. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Throughout the program emphasis was on pure products rather than improved yields.

***p*-Iodobenzyl Alcohol (7).** A mixture of 1350 ml of glacial acetic acid and 250 g (0.98 mol) of iodine was heated to 100 °C and concentrated sulfuric acid (140 ml) added rapidly, followed by the addition of 216 g (2 mol) of benzyl alcohol. While maintaining the temperature at 100–110 °C, a solution of 92 g (0.5 mol) of sodium iodate in 500 ml of water was added dropwise over a period of 1 h. The reaction was heated for an additional 30 min and then poured onto 1 kg of cracked ice. After extracting with chloroform, the chloroform was evaporated to give crude **6**. Treatment with 10% methanolic potassium hydroxide (400 ml) and water (200 ml) for 1.5 h at 70–80 °C gave **7** which was extracted with chloroform, dried (magnesium sulfate), and evaporated to a solid. Distillation gave 206 g (0.88 mol) of **7** that could be further purified by recrystallization from hexane: mp 71.8–73.4 °C; ir 3220 cm^{-1} (br, OH); NMR δ 4.18 (s, 2 H, CH_2), 4.52 (s, 1 H, OH), and 7.02 (2 d, 4 H, 1,4-Ph); mass spectrum *m/e* (measured mass) 233.9545 (calculated for C_7H_7IO, 233.9544).[24] Anal. C, H, I.

p-Iodophenylpropanol (**37**) was similarly prepared from 3-phenylpropanol (Aldrich): bp 112 °C (0.4 mmHg); $n^{25}D$ 1.6048; ir 3320 cm^{-1} (br, OH); NMR δ 1.70 (pent, 2 H, CH_2CH_2OH), 2.52 (t, 2 H, $PhCH_2$), 3.52 (m, 3 H, CH_2OH), 7.05 (2 d, 4 H, 1,4-Ph). Anal. ($C_9H_{11}IO$) C, H, I.

***n*-Amyl-*p*-iodobenzyl Carbonate (25).** Phosgene was bubbled into a flask containing 50 ml of toluene at 0 °C until a weight gain of 15 g (0.07 mol) had been obtained. A solution of 23.2 g (0.1 mol) of **7** in 50 ml of toluene was added and after 30 min at 0 °C, followed by 2 h at room temperature, the toluene was removed at a reduced pressure and a temperature not exceeding 60 °C. This gave a concentrated solution of **8**. A solution of 69 g (0.79 mol) of *n*-amyl alcohol in 320 ml of pyridine was cooled to −3 °C and **8** in chloroform (300 ml) was added dropwise. The reaction was warmed to room temperature and stirred for 1 h. Next 800 ml of 6 N hydrochloric acid and the reaction mixture were added simultaneously to well-stirred 3 N hydrochloric acid (400 ml) and cracked ice (800 g). The lower organic phase was removed and the aqueous phase extracted with chloroform. The combined chloroform was dried (magnesium sulfate) and evaporated to an oil. Distillation at reduced pressure gave 12 g (0.033 mol) of **25** (44% yield): bp 145–150 °C (0.3 mmHg); $n^{25}D$ 1.5439; ir 1740 (C=O), 1250 cm^{-1} (OC=OO); NMR δ 4.09 (m, 2 H, OCO_2CH_2), 5.02 (s, 2 H, $PhCH_2OCO_2$); mass spectrum *m/e* (measured mass) 348.0231 (calculated for $C_{13}H_{17}IO_3$, 348.0225).[24] Anal. C, H, I.

Similarly prepared from the appropriate starting iodinated alcohol and aliphatic alcohol were **23** [Anal. ($C_{12}H_{15}IO_3$) C, H, I], **24** [Anal. ($C_{11}H_{13}IO_4$) C, H, I], **27** [Anal. ($C_{14}H_{19}IO_3$) C, H; I: calcd, 35.05; found, 35.64], **28** [Anal. ($C_{14}C_{19}IO_3$) C, H, I], **30** [Anal. ($C_{16}H_{23}IO_3$) C, H, I], **31** [Anal. ($C_{16}H_{23}IO_3$) C, H, I], **32** [Anal. ($C_{14}H_{17}IO_5$) C, H, I], **33** [Anal. ($C_{18}H_{27}IO_3$) C, H, I], **42** [Anal. ($C_{14}H_{19}IO_3$) C, H, I], and **45** [Anal. ($C_{16}H_{23}IO_3$) C, H, I].

***p*-Iodobenzyl-*n*-hexyl Carbonate (26).** A solution of 12 g (0.05 mol) of **7** in 50 ml of chloroform and 8.75 ml of pyridine was cooled to 0 °C and 8.5 ml of *n*-hexyl chloroformate in 25 ml of chloroform was added dropwise while maintaining the temperature below 0 °C. After completing the addition, the reaction was heated at reflux for 30 min. The cooled reaction was extracted with chloroform and the chloroform washed with 5% hydrochloric acid and water. After drying (magnesium sulfate), the chloroform was evaporated and the colorless oil vacuum distilled [169–171 °C (0.25 mmHg)] to give 15.2 g (0.42 mol) of **26**: $n^{25}D$ 1.5332; ir 1730 (C=O), 1230 cm^{-1} (OC=OO); NMR δ 4.05 (m, 2 H, OCO_2CH_2), 4.97 (s, 2 H, $PhCH_2OCO_2$); mass spectrum *m/e* (measured mass) 362.0362 (calculated for $C_{14}H_{19}IO_3$, 362.0381).[24] Anal. C, H, I.

Similarly prepared from the appropriate starting iodinated alcohol and either ethyl chloroformate, *n*-hexyl chloroformate, or *n*-octyl chloroformate were **5** [Anal. ($C_{13}H_{17}IO_3$) C, H, I], **21** [Anal. ($C_{15}H_{21}IO_3$) C, H, I], **29** [Anal. ($C_{16}H_{23}IO_3$) C, H, I], **35** [Anal. ($C_{11}H_{13}IO_3$) C, H, I], **36** [Anal. ($C_{15}H_{21}IO_3$) C, H, I], **38** [Anal. ($C_{12}H_{15}IO_3$) H; C: calcd, 43.11; found, 42.36], **39** [Anal. ($C_{16}H_{23}IO_3$) C, H, I], **41** [Anal. ($C_{13}H_{17}IO_3$) C, H, I], **43** [Anal. ($C_{17}H_{25}IO_3$) C, H, I], **44** [Anal. ($C_{14}H_{19}IO_3$) H, I; C: calcd, 46.40; found, 45.81], **46** [Anal. ($C_{18}H_{27}IO_3$) C, H, I], **48** [Anal. ($C_{20}H_{31}IO_3$) C, H, I], **49** [Anal. ($C_{16}H_{23}IO_3$) C, H, I], **50** [Anal. ($C_{14}H_{18}I_2O_3$) C, H, I], **51** [Anal. ($C_{14}H_{18}I_3NO_3$) C, H, I], and **52** [Anal. ($C_{16}H_{20}I_3NO_4$) C, H, I].

***p*-Iodophenethyl Alcohol (34).** Phenethyl acetate (Pfaltz and Bauer) was subjected to the iodination procedure as outlined in the preparation of **7**. *p*-Iodophenethyl alcohol was isolated in a 52% yield: bp 110–120 °C (0.5 mmHg); $n^{25}D$ 1.6155; ir 3330 cm^{-1} (br, OH); NMR δ 2.6 (m, CH_2, $PhCH_2$), 3.38 (s, 1 H, OH), 3.55 (t, 3 H, CH_2O), 7.14 (2 d, 4 H, 1,4-Ph); mass spectrum *m/e* (measured mass) 247.9685 (calculated for C_8H_9IO, 247.3700).[24] Anal. C, H, I.

3-(*p*-Iodophenyl)butanol (40). Crotyl alcohol (Aldrich) was condensed with benzene using aluminum chloride according to

a known procedure.[26] 3-Phenylbutanol was then iodinated as outlined for the preparation of **7**. Recovered **40** gave bp 137 °C (0.7 mmHg); $n^{25}D$ 1.5964; ir 3340 cm^{-1} (br, OH); NMR δ 1.2 (d, 3 H, CH_3), 1.68 (qt, 2 H, CH_2), 2.77 (m, 1 H, CH), 3.47 (m, 3 H, CH_2OH), 7.2 (2 d, 4 H, 1,4-Ph); mass spectrum *m/e* (measured mass) 275.9993 (calculated for $C_{10}H_{13}IO$, 276.0013).[24] Anal. C, H, I.

2-(*p*-Iodobenzyl)butanol (14). A mixture of 156 g (1.5 mol) of benzaldehyde, 200 g (1.6 mol) of potassium butyrate, and 600 ml of butyric anhydride was stirred and heated at 120 °C for 40 h under a nitrogen atmosphere. After cooling to room temperature, 750 ml of water was added and the reaction acidified with hydrochloric acid. This mixture was steam distilled with ca. 500 ml of distillate collected. On cooling, a solid formed in the distillation pot. This was collected and recrystallized from water to give 116 g (0.66 mol) of **10** (44% yield): mp 104–104.8 °C (lit.[22] mp 104 °C).

A solution of 35.2 g (0.2 mol) of **10** in 450 ml of 3% sodium hydroxide was hydrogenated at an initial pressure of 60 psi using 4 g of 5% palladium on charcoal. After consumption of the theoretical amount of hydrogen, the solution was filtered, neutralized with hydrochloric acid, and extracted with ether. After drying (magnesium sulfate), the ether was evaporated to give 34 g (0.19 mol) of **11**: ir 2960 (br, CO_2H), 1700 cm^{-1} (C=O); NMR δ 0.90 (t, J = 6 Hz, 3 H, CH_3), 1.47 (qt, J = 6 Hz, 2 H, CH_2CH), 2.68 (m, 3 H, CH_2CH), 7.08 (s, 5 H, PhH), 12.09 (s, 1 H, CO_2H).

α-Ethylhydrocinnamic acid was converted to its ethyl ester using a known procedure.[27] The crude ester was recovered as a red-brown oil and converted to **14** without further purification.

Using lithum aluminum hydride, the ester was converted to **12** by a known procedure.[28]

Recovered **12** was then converted to **14** using the procedure for the preparation of **7**. Compound **14** gave bp 134–137 °C (0.2 mmHg); $n^{25}D$ 1.5886; ir 3320 cm^{-1} (br, OH); NMR δ 0.90 (t, 3 H, CH_3), 1.30 (m, 3 H, $CHCH_2CH_3$), 2.50 (d, 2 H, $PhCH_2$), 2.88 (s, 1 H, OH), 3.40 (d, 2 H, CH_2OH), 7.10 (2 d, 4 H, 1,4-Ph); mass spectrum *m/e* (measured mass) 290.0140 (calculated for $C_{11}H_{15}IO$, 290.0169).[24] Anal. C, H, I.

Using hexanoic anhydride and sodium hexanoate, as obtained by standard procedures,[16] **47** was prepared by the above process: bp 140 °C (0.1 mmHg); $n^{25}D$ 1.5446; ir 3300 cm^{-1} (br, OH); NMR δ 0.90 (m, 3 H, CH_3), 1.30 [m, 7 H, $-CH(CH_2)_3-$], 2.54 (d, 2 H, $PhCH_2$), 3.13 (s, 1 H, OH), 3.40 (d, 2 H, CH_2OH), 7.18 (2 d, 4 H, 1,4-Ph); mass spectrum *m/e* (measured mass) 318.0470 (calculated for $C_{13}H_{19}IO$, 318.0482).[24] Anal. C, H, I.

3-Amino-2,4,6-triiodobenzyl Alcohol (17). 3-Aminobenzoic acid was converted to 3-aminobenzyl alcohol, mp 90.6–93.2 °C (lit.[30] mp 91 °C), using boron methyl sulfide.[29] Iodination of 3-aminobenzyl alcohol with iodine monochloride gave **17** in a 76% yield: mp 149.8–151.2 °C (lit.[19] mp 150 °C). Anal. ($C_7H_6I_3NO$) C, H, I.

3-Acetamido-2,4,6-triiodobenzyl Alcohol (18). Treatment of **17** with acetic anhydride and a trace of sulfuric acid gave **18** in good yield: mp 254.2–256.0 °C. Anal. ($C_9H_8I_3NO_2$) C, H, I.

3,5-Diiodobenzyl Alcohol (16). 2,3,5-Triiodobenzoic acid was treated with lithium aluminum chloride to give **16** in a 67% yield: mp 136.5–140 °C (lit.[18] mp 137 °C).

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