Kirk-Othmer Encyclopedia of Chemical Technology.

RADIOPAQUES

Medical examination of soft tissues or organs by nonsurgical means often requires the introduction of a special agent which makes the detection system responsive to detail in the tissue of interest. Diagnostic imaging agents include those used in magnetic resonance, ultrasound, radionuclide imaging, and x-ray technology (qv) (see Medical imaging technology). Radiopaques for x-ray imaging, more commonly called x-ray contrast media or radiographic contrast agents, are examples of such diagnostic agents. These chemicals absorb x-rays strongly. When they accumulate in the target area, they create a contrast in the x-ray image thereby permitting visual examination of the target organ. Hence the classification as contrast agents or contrast media.

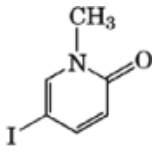
Absorption of x-radiation is an atomic phenomenon related to the atomic number of the absorbing atom (1) such that the heavier elements are, in general, more efficient at absorbing x-rays. Except for barium sulfate [7727-43-7], all other radiopaque agents in use as of the mid-1990s are organic derivatives of iodine. The iodine atoms function as the x-ray absorbers, and the organic moiety can be manipulated to provide desirable characteristics of a contrast agent and to decrease toxicity and physiological side-effects. Table 1 contains a summary of the more important radiographic procedures and contrast agents for x-ray visualization of various tissues and organs.

1. Angiography and Urography

Angiographic contrast media (CM) are administered intravascularly for the radiographic visualization of blood vessels to evaluate vascular abnormalities. Uses include cerebral, coronary, pulmonary, renal, visceral, and peripheral arteriography, aortography, ventriculography, and venography. Because of the very high concentrations of contrast media required for angiography, such materials must have high water solubility. More dilute formulations of these same agents are used for urography. In urographic procedures, the CM are injected intravenously and their excretion via the kidneys is visualized radiographically as an evaluation of renal function (excretory urography). Alternatively, the CM are instilled via catheters directly into the lower urinary tract (retrograde pyelography). Excretory urography is the more common procedure. Following intravascular administration, the angiographic–urographic CM are distributed in the extracellular space and subsequently excreted unchanged, principally in the urine.

The historical development of angiographic–urographic CM (2) proceeded from inorganic forms of strontium bromide through sodium iodide and thorium dioxide to organic compounds. The inorganic bromide and iodide compounds produced painful and life-threatening adverse reactions. The radioactive nature of thorium resulted in severe but delayed effects, eg, liver cancer. Attempts to eliminate the adverse effects resulting from iodide ions, yet keep the heavy atom x-ray opacity of iodine, led to the consideration of iodinated organic compounds. Because the chemotherapeutic drug Selectan [60154-05-4] **1** was iodinated and known to be excreted in the urine, it was tested as an intravenous urographic agent and proved to give adequate pictures (3). An improved derivative of Selectan called Uroselectan [80462-95-9] **2** followed (3). Then iodopyracet [300-37-8] **3** and sodium iodomethamate [519-26-6] **4**, each containing two iodine atoms per molecule for higher radiographic

efficacy, were widely used in the 1930s and 1940s (4–6). Sodium methiodal [126-31-8], ICH_2SO_3Na, was also in clinical use for a time (7).



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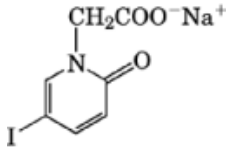

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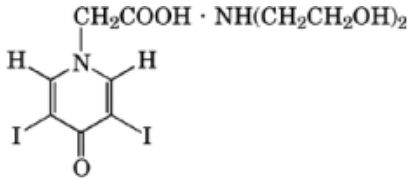

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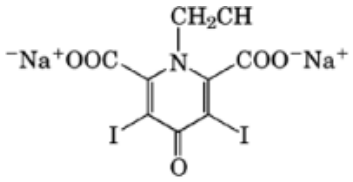

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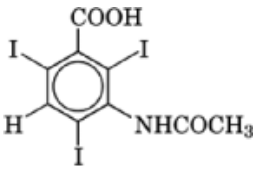
1.1. High Osmolality Contrast Media

An important advance in radiopaques came with the synthesis of aminotriiodobenzoic acid and its acetylated derivative, acetrizoic acid [85-36-9] **5** (8, 9). Aqueous solutions of sodium acetrizoate possessed the thermal stability so that they could be autoclaved (10) with minimal decomposition. The higher iodine content, ie, 3 atoms/molecule, increased the contrast efficiency, and the clinical safety of acetrizoate was improved over that of the earlier urographic agents.



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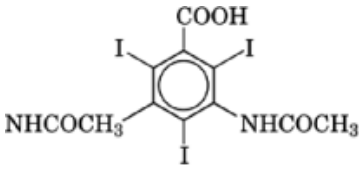

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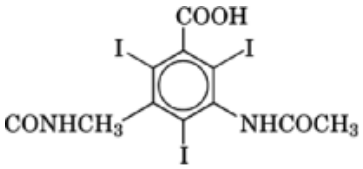

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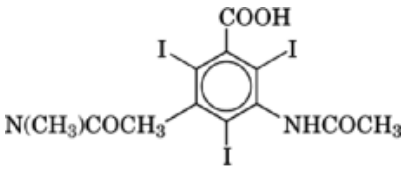

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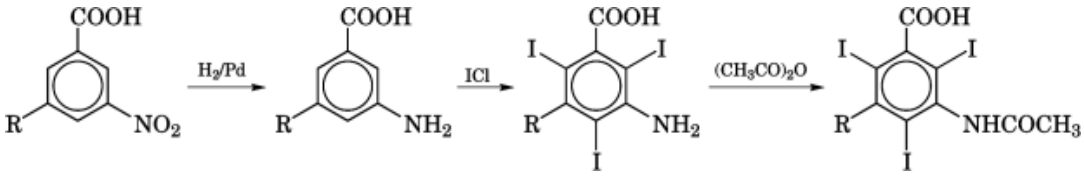
Further improvements in the late 1950s and early 1960s led to the development of three derivatives of acetrizoate that comprise a group of important angiographic and urographic ionic contrast media: diatrizoic acid [117-96-4] **6**, iothalamic acid [2276-90-6] **7**, and metrizoic acid [1949-45-7] **8**. These compounds, in which the hydrogen on the ring is replaced by more hydrophilic moieties, were found to be less toxic than acetrizoate, because modification made them less amenable to protein binding. The preparations of these compounds are straightforward and cost efficient. Starting with a derivative of nitrobenzoic acid, reduction of the nitro group to an amine is followed by iodination and acylation. The R group can be chemically altered in the reaction sequence, depending on the substitution requirements (10, 11).



These ionic contrast media are synthesized and purified as free acids. As such, they are highly insoluble in water, which facilitates isolation and purification. In commercial formulations, these compounds are prepared

Table 1. Radiographic Procedures and Corresponding Radiopaques

Procedure	Organ/region	Radiopaque agents
angiography	blood vessels	sodium or meglumine salt of diatrizoic acid, iothalamic acid, metrizoic acid, and ioxaglic acid; iopamidol, iohexol, ioversol, iopromide, iomeprol, iopentol, ioxilan, iobitridol
arteriography	arteries	
aortography	aorta	
ventriculography	ventricles of the heart	
venography (phlebography)	veins	
urography	urinary tract	
computed tomography	body, head	
myelography	subarachnoid space of the spinal cord	meglumine salt of iothalamic acid[a] and iocarmic acid[a]; metrizamide,[a] iohexol, iopamidol, iotrol, iodixanol
cholecystography	gallbladder	iopanoic acid, iocetamic acid, sodium or calcium iopodate, sodium tyropanoate, meglumine iodipamide, ioglycamide, iodoxamate
cholangiography	bile ducts	
gastrointestinal radiography	alimentary tract	barium sulfate, sodium or meglumine diatrizoate, iohexol
arthrography	joints	meglumine diatrizoate, meglumine iothalamate, sodium and meglumine salt of ioxaglic acid, iohexol ethiodol, meglumine diatrizoate-meglumine iodipamide mixture, sodium and meglumine salts of
hysterosalpingography	uterus and fallopian tubes	iothalamic, diatrizoic and ioxaglic acids, iohexol

[a] Not commonly used as of the mid-1990s.

as sodium or meglumine salts in order to provide solubility. Sequestering agents such as EDTA are added to bond to trace inorganic impurities that can cause catalytic deiodination (12). Buffers may also be included to ensure physiological pH conditions (12). Table 2 contains the important physical and biological (intravascular LD_{50}, median lethal dose) properties of the ionic agents.

Osmolality, a measure of the number of particles in a solution, is approximately proportional to the sum of the concentrations of all molecular and ionic particles present. As shown in Table 2, the osmolality of ionic monomers is about 1500 mOsm/kg at concentrations of 280–300 mg/mL on a mg of iodine basis. These ionic compounds dissociate into sodium or meglumine cations and the benzoate anions. Each ion contributes to the overall osmolality of the diagnostic solution in a ratio of three iodine atoms delivered as two particles, the cation and the anion. In the range of concentrations required for good x-ray visualization, the high osmolality of these ionic agents relative to plasma, which has an osmolality of approximately 300 mOsm/kg H_2O (17, 18), and surrounding tissues causes leaching of water across semipermeable membranes, resulting in undesirable physiological effects (19, 20). Hence, this class of agents is known as high osmolality contrast media (HOCM), or ratio-1.5 CM, ie, three iodines per two particles. Clinical trials indicate that many adverse effects owing to ionic agents can be attributed to high osmolality (18–29). Such effects include vasodilation, hemodilution, crenation of red blood cells, and disruption of endothelial integrity. The pain and heat sensation generated upon intravascular injection of the ionic agents has been correlated with the vasodilation and vascular endothelial damage induced by the high osmolality of the contrast solutions (25, 30, 31).

1.2. Low Osmolality Contrast Media

An ideal intravascular CM possesses several properties: high opacity to x-rays, high water solubility, chemical stability, low viscosity, low osmolality, and high biological safety. Low cost and patentability are also important for commercial agents. The newer nonionic and low osmolar agents represent an advanced class of compounds in the development of x-ray contrast media.

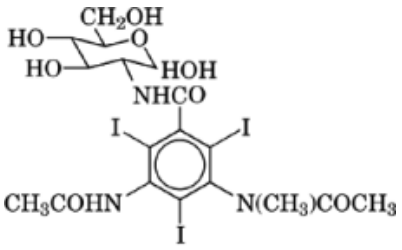
Table 2. Properties of Ionic Monomeric Radiopaques for Angiography and Urography

Name						
Generic	Trade	Company name	Iodine concentration, 60% wt/vol, mg/mL	Osmolality, mOsm/kg H_2O	LD_{50}, iv mice g/kg[a]	Ref.
acetrizoate sodium	Urokon	Mallinckrodt Chemical Works			5.5	6
diatrizoate meglu-mine	Angiovist, Reno-M-60, Hypaque-M 60	Berlex Labs, Squibb Diagnostics[b] Sterling-Winthrop Pharma-ceuticals[c]	282	1400, 1500	8.4[d]	13
diatrizoate meglu-mine 52%/sodium (8%)	MD-60, Renografin-60	Mallinckrodt Medical, Squibb Diagnostics[c]	292	1420,[e] 1539[f]		13
iothalamate meglu-mine	Conray	Mallinckrodt Medical	282	1400	8.0[g,h] 11.5[g,i]	16
metrizoate meglu-mine			278	1660	9.1[h,j]	

[a] Grams of iodine per kilogram of body weight.
[b] Bracco Diagnostics, as of 1996.
[c] Nycomed Imaging, as of 1996.
[d] Value is for diatrizoate sodium 6.
[e] Value for Renografin-60.
[f] Value for MD-60.
[g] Values are for iothalamate sodium.
[h] Ref. 14.
[i] Ref. 15.
[j] Value is for metrizoate sodium Isopaque, Sterling-Winthrop Pharmaceuticals 14.

Development of nonionic compounds to eliminate ionicity, reduce osmolality, and hence minimize adverse effects, such as painful reactions associated with the injection of ionic agents, was proposed in 1968 (22, 32). These triiodobenzene derivatives contain no ionizable carboxyl moiety, and their high water solubility and biological safety are achieved by employment of highly polar, hydrophylic groups. Because these compounds do not dissociate in solution, approximately half the osmolality of the ionic agents results at equivalent concentrations. Therefore, these nonionic agents are referred to as low osmolality contrast media (LOCM) or ratio-3 CM, ie, three iodine atoms per particle.

Introduced in 1975, metrizamide [31112-62-6] **9** was the first clinically successful nonionic agent (33). It possesses lower subarachnoid and acute intravascular toxicity than the ionic agents and was used for myelographic applications. However, this compound is unstable under autoclaving conditions in aqueous solution and therefore requires dispensing as a lyophilized powder which must be reconstituted prior to use. Intensive research in the 1970s and 1980s produced safer and more stable agents, eg, iopamidol [60166-93-0] **10** (26, 34–37), iohexol [66108-95-0] **11** (28, 37–40), and ioversol [87771-40-2] **12** (29, 41). These three nonionic LOCM have become the primary products utilized for angiographic–urographic procedures.



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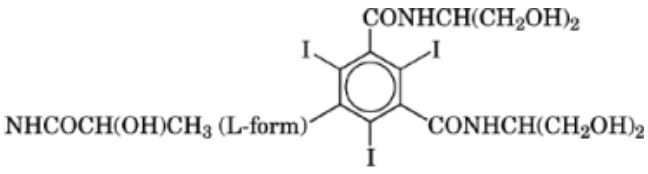

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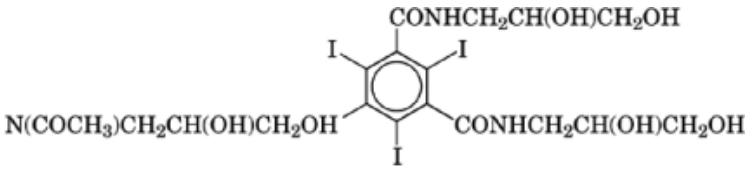

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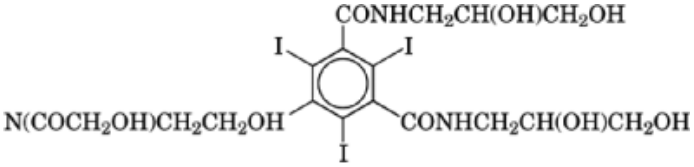


(**12**)

Tables 3 and 4 summarize the important properties of the LOCM in use or under development as of this writing (ca 1996). As shown in Table 4, these agents provide lower osmolality, approximately 550–700 mOsm/kg at 300 mg/mL on a mg of iodine basis, and reduced toxicity relative to the ionic monomeric agents (see Table 2). Clinical studies (17–20, 26, 28, 29, 64–67) have demonstrated that the nonionic agents offer a significant margin of safety, have fewer side effects, and provide a much-improved level of comfort to the patients, compared to the ionic species. The increased hydrophilicity of these LOCM also contributes to a reduction in adverse physiological effects by limiting binding to proteins and other biomolecules (17, 43, 58, 68–70). The partition coefficient data in Table 4 reflect the correlation between hydrophilicity and intracisternal neurotoxicity. The more hydrophilic agents, ie, those having the lower octanol/water partition coefficients, are generally less neurotoxic.

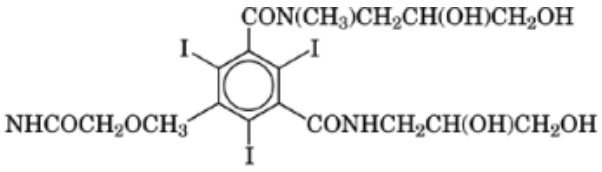
Contrast materials of low osmolality can be classified into three chemical types: (*1*) nonionic monomers, such as iopamidol, iohexol, ioversol, iopromide [73334-07-3] **13** (71), iomeprol [78649-41-9] **14** (42), iopentol [89797-00-2] **15** 51, ioxilan [107793-72-6] **16** 53, 60, 63, and iobitridol [136949-58-1] **17** 72; (*2*) monoionic

Table 3. Properties of Low Osmolality Contrast Media (LOCM) for Angiography and Urography[a]

Name						Viscosity,[b] 300 mg/mL, cps	
Generic	Trade	Company Name	Molecular weight	Iodine content, %	Solubility in water, % wt/vol	20°C	37°C
metrizamide	Amipaque	Sterling-Winthrop Pharmaceuticals[c]	789.10	48.2	80 35	11.7 (42)	6.2 (43)
iopamidol	Isovue	Squibb Diagnostics[d]	777.09	49.0	89 35	8.8 (44)	4.7 (44)
iohexol	Omnipaque	Winthrop Pharmaceuticals[c]	821.14	46.4	>120 45	11.8 (46)	6.3 (46), 5.6 (47)
ioversol	Optiray	Mallinckrodt Medical	807.12	47.2	>125 (48)	8.2[e] (49)	5.5 49
iopromide	Ultravist	Berlex Labs	791.12	48.1		8.7 (50)	4.8 (43)
iomeprol	Iomeron	Bracco	777.09	49.0	>100 (42)	7.5 (42)	4.2 (42)
iopentol	Imagopaque	Nycomed Imaging	835.17	45.6	100 (51)	13.2 (52)	6.5 (52)
ioxilan	Oxilan	Cook Imaging	791.12	48.1			4.9 (53)
iobitridol	Xenetix	Guerbet Laboratory	835.17	45.6			6.0 (47)
ioxaglic acid, meglumine, and sodium salts	Hexabrix	Mallinckrodt Medical and Guerbet Laboratory	1268.90	60.0		15.7[f] (54)	7.5[f] 54

[a] References cited are given in parentheses.
[b] Readings are on a weight of iodine per volume of solution basis; cps = cycles per second of viscometer.
[c] Nycomed Imaging, as of 1996.
[d] Bracco Diagnostics, as of 1996.
[e] Viscosity reading at 25°C.
[f] Viscosity readings at 320 mg/mL on a weight of iodine basis.

dimers, such as ioxaglic acid [59017-64-0] **18** 27, 73; and *3* nonionic dimers, iotrolan [79770-24-4] and iodixanol [92339-11-2], both of which are being investigated for intravascular and intrathecal (myelographic) uses.



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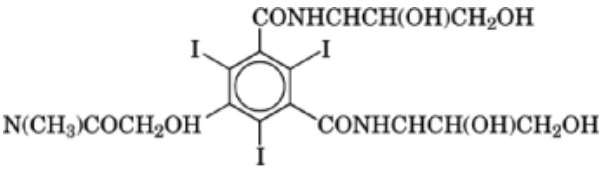

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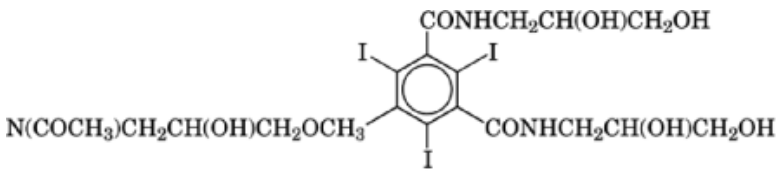
Table 4. Osmolality, Toxicity, and Partition Coefficients of LOCM for Angiography and Urography[a]

Name					LD_{50}[b]		
Generic	Trade	Company name	Concentration,[b] mg/mL	Osmolality, mOsm/kg H_2O	Intravascular, mice g/kg	Intracisternal[c], rats mg/kg	Partition coefficient, octanol/water, $\times 10^4$
metrizamide	Amipaque	Sterling-Winthrop Pharmaceuticals[d]	300	490 43	15 (33,55) 12.1 (57)	150 (48,56)	190 (56) 390[e] (58)
iopamidol	Isovue	Squibb Diagnostics[f]	250	520 44	21.8 (35,59)	800 (48,56)	19 (56)
			300	620 (44)	17 (48)		25 (52)
			370	800 (44)	17–18.5 (53) 16.4 57		38[e] (58)
iohexol	Omnipaque	Winthrop Pharmaceuticals[d]	240	520 46	23.4 (40)	977 (48,56)	8 (56)
			300	670 (46) 690 (47)	15 (48) 17 (47)		10 (52) 19[e] (58)
			350	840 46	17.9 (53) 18.5 (59)		
ioversol	Optiray	Mallinckrodt Medical	240	500 (49)	20 (41)	>1200 (48,56)	4 (56)
			300	650 (49)	16 (48)		10[e] (58)
			320	700 49	19.6 (59)		
			350	790 (49)			
iopromide	Ultravist	Berlex Labs	300	610 (60)	11.5–13.0 (53)	122 (61)	89[e] (58)
			350	760 60	16.5 (57) 18.5 (59)		
iomeprol	Iomeron	Bracco	250	450 (42)	19.9 (59)		
			300	540 (42)			
			350	630 (42)			
iopentol	Imagopaque	Nycomed Imaging	300	640 (52) 660 (51)	22 (51) 19.5 (62)		70 (52)
			350	810 (52)	15.7 (59)		
ioxilan	Oxilan	Cook Imaging	300	560 (63)	18.8 (53)		
			350	690 (63)			
iobitridol	Xenetix	Guerbet Laboratory	300	695 (47)	16.8 (47)		
ioxaglic acid, meglumine, and sodium salts	Hexabrix	Mallinckrodt Medical and Guerbet Laboratory	320	600 (54)	13.5 (32) 10.2 59		10[e] (58)

[a] References cited are given in parentheses.
[b] Values given are on a weight of iodine basis.
[c] Describes administration of CM into the cisterna magna to assess the neurotoxicity of the CM.
[d] Nycomed Imaging, as of 1996.
[e] These partition coefficient data were derived from the log *P* values reported therein.
[f] Bracco Diagnostics, as of 1996.



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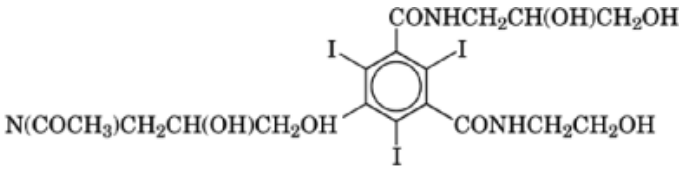

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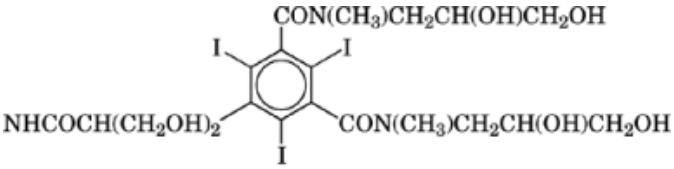

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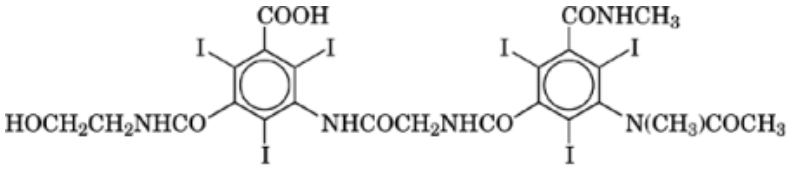

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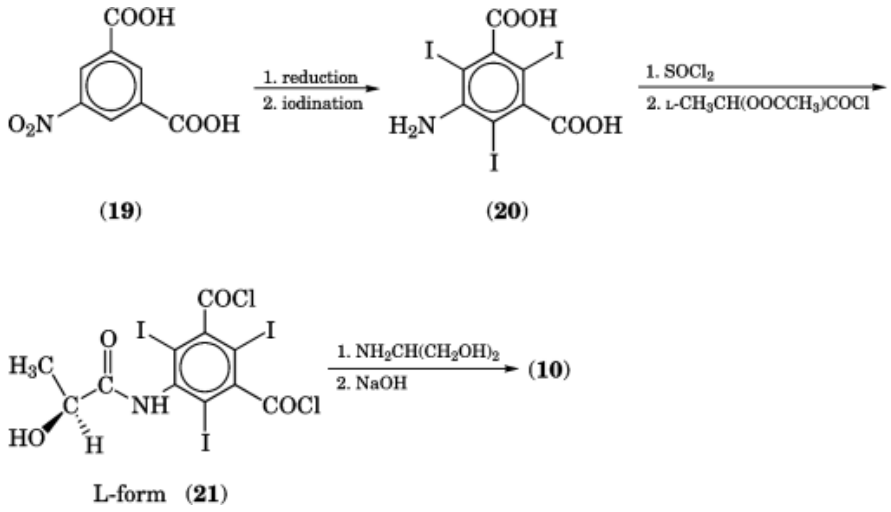
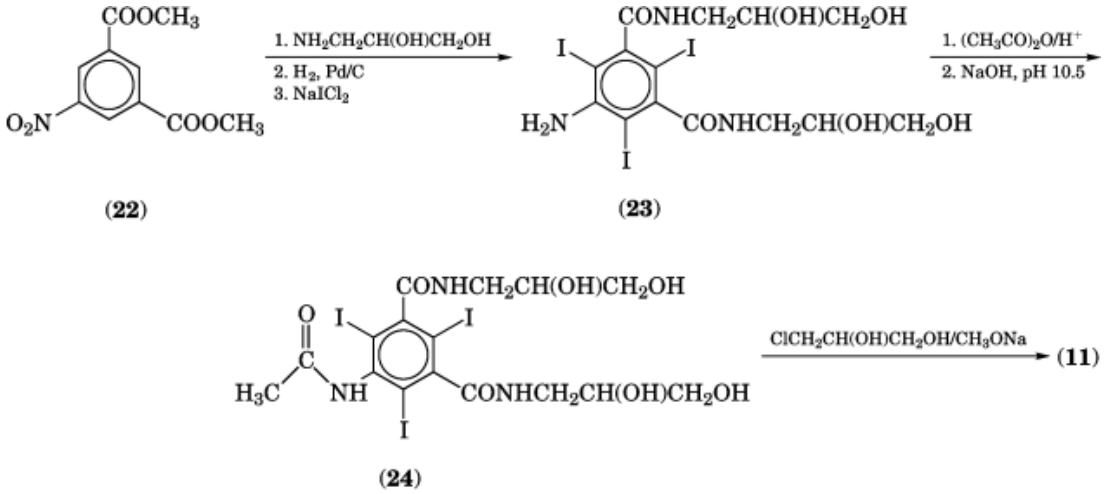
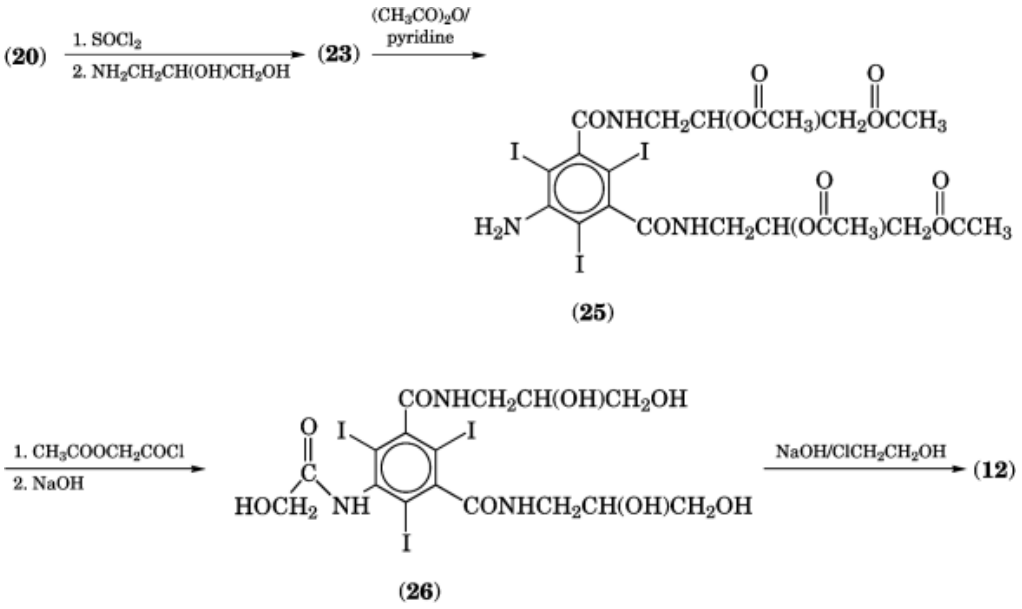
All nonionic contrast media used as of the mid-1990s are amide derivatives of triiodinated 5-aminoisophthalic acid. Therefore, 5-nitroisophthalic acid **19** serves as the starting material and, after reduction and iodination, the intermediates are chemically manipulated to provide the desired final products. The general preparation of triiodoisophthalamide radiopaque agents 74 is illustrated by the syntheses of iopamidol, iohexol, ioversol, and ioxaglic acid. In the synthesis of iopamidol **10** 26, 35, reduction of 5-nitroisophthalic acid yields the corresponding amino diacid, which is then iodinated to give 5-amino-2,4,6-triiodoisophthalic acid **20**. Activation of the aromatic nucleus by the amino group is required for the iodination. Treatment of the latter with thionyl chloride results in the dichloride, which is subjected to *N*-acylation with L-2-acetoxypropionyl chloride (*S*-configuration) to afford the diacid chloride **21**. Amidation of **21** with 2-amino-1,3-propanediol (serinol) followed by hydrolysis of the ester group using aqueous sodium hydroxide gives iopamidol **10**.



Iohexol **11** is prepared 39, 40 starting with aminolysis of the nitro-diester **22**, which is prepared by esterification of the nitro-diacid **19**. Reduction of the nitro group followed by iodination of the resulting amino-diamide gives the key triiodinated intermediate **23**. Peracylation of **23** using acetic anhydride and catalytic amounts of sulfuric acid followed by saponification of the *O*-acyl groups with aqueous sodium hydroxide produces the acetamido compound **24**. N-Alkylation of compound **24** using 3-chloro-1,2-propanediol in the presence of sodium methoxide yields iohexol **11**.



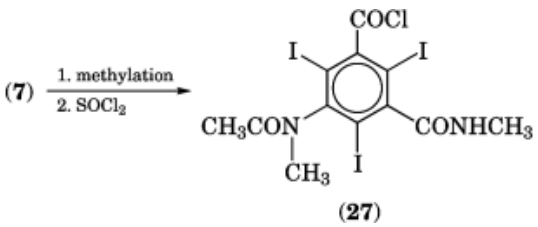
In the preparation of ioversol **12** 41, the key intermediate **23** is prepared from the diacid **20** by the action of thionyl chloride followed by 3-amino-1,2-propanediol. The alcohol groups of **23** are protected as the acetates **25**, which is then N-acylated with acetoxyacetyl chloride and deprotected in aqueous methanol with sodium hydroxide to yield **26**. N-alkylation of **26** produces ioversol **12**.



The final step in the preparation of both iohexol and ioversol involves some very interesting chemistry, ie, the N-alkylation of an acylamino-triiodoisophthalamide. Derivatizing the aromatic core, particularly using hydrophilic groups, confers desired properties such as water solubility for angiographic agents.

The steric bulk of the three iodine atoms in the 2,4,6-triiodobenzene system and the amide nature of the 1,3,5-substituents yield rotational isomers of the 5-*N*-acyl-substituted 2,4,6-triiodoisophthalamides. Rotational motion in the bonds connecting the side chains and the aromatic ring is restricted. These compounds also exhibit stereoisomerism when chiral carbon atoms are present on side chains. (*R*,*S*)-3-Amino-1,2-propanediol is incorporated in the synthesis of iohexol **11** and ioversol **12** and an (*S*)-2-hydroxypropanoyl group is used in the synthesis of iopamidol **10**. Consequently, the resulting products contain a mixture of stereoisomers, ie, *d,l*-pair and meso-isomers, or an optical isomer.

Ioxaglic acid **18**, a monoionic dimer, is also widely used in angiographic–urographic applications. Because it contains six iodine atoms in two dissociated particles, **18** is classified as a ratio-3 LOCM. The key steps of its synthesis are as follows 73:



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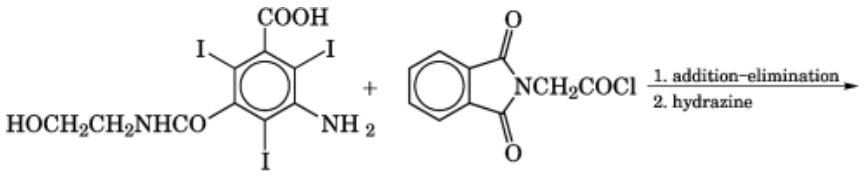
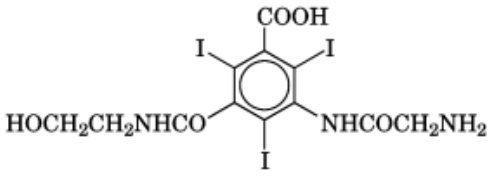




(28)

(27) + **(28)** ⟶ **(18)**

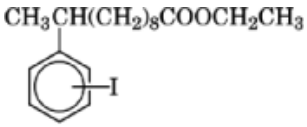
1.3. Economic Considerations

The accumulation of clinical and animal data over many years has resulted in a universal consensus that LOCM are safer and cause less patient discomfort than HOCM (17–20,26–29,64–67,70,75). Although all research efforts are directed toward LOCM, these remain substantially more expensive than the HOCM 17. The LOCM are fundamentally more difficult to synthesize and purify and, therefore, more expensive to manufacture. The expenses associated with the research and development of new drugs are substantial. Licensing fees and royalties paid to the companies owning the LOCM patents inflict additional cost. These factors make LOCM 10–20 times more expensive than HOCM 65, 75. Until cost can be reduced, the main benefit of LOCM may be to provide an additional margin of safety to those patients at higher risk 19. However, the LOCM reduce the risk of all levels of adverse reactions 66, not just those that are life-threatening. Thus, managing the adverse reactions of HOCM can become more costly than simply curtailing adverse reactions to CM by routine use of LOCM 75.

2. Myelography

The administration of a contrast agent into the subarachnoid space permits delineation of the spinal cord and is used for diagnosis of diseases of the nervous system and spinal canal 76. As early as 1919, air or other gases were used to provide negative contrast. Because gases are inadequately miscible with cerebrospinal fluid (CSF), large amounts of CSF had to be removed for the gas to occupy the space and effectively define the region. The occurrence of severe side effects and visualization restrictions contraindicates gas myelography.

Development of positive contrast material for myelography began with water-insoluble radiographic agents such as bismuth salts, colloidal silver, thorium dioxide, iodinated poppyseed oil, and the oil-based iophendylate [1320-11-2] (Pantopaque) **29**. Because of high density and viscosity, iophendylate forms a cohesive oily mass that does not mix with CSF and can be repositioned by the action of gravity. Incomplete penetration of iophendylate around nerve roots and other narrow crevices may, however, produce inadequate definition. After the procedure, the iophendylate is removed as much as possible by aspiration. Any remaining material is absorbed very slowly, tending to remain fixed in position, and can produce chronic tissue irritation.



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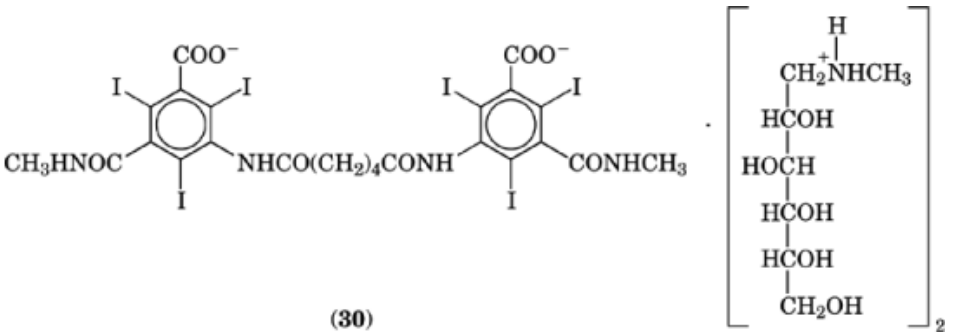
Water-soluble contrast media (CM) are preferred because of effective mixing with CSF, plus the radiopaque is absorbed and effectively excreted in the urine, and does not have to be physically removed from the subarachnoid space after the procedure. Sodium methiodal, the first water-soluble agent used for myelography, produced neurotoxicity problems when exposed to the cells of the spinal cord and brain, thus limiting utility to the lumbar region and requiring the application of spinal or general anesthesia.

Soon after iothalamic acid **7** was introduced as a urographic–angiographic agent, it was recognized that its meglumine salt produced fewer neurotoxic effects than sodium methiodal, and iothalamate meglumine replaced sodium methiodal in myelographic procedures. The meglumine salt of iocarmic acid [54605-45-7] **30** also demonstrated decreased neurotoxicity 77. These two ionic agents were used extensively throughout the 1970s.



(30)

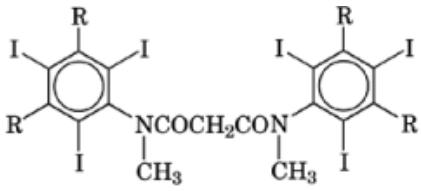
Iothalamate meglumine and iocarmate meglumine, both used clinically, are accompanied by significant adverse effects, such as muscle spasms and convulsions. These effects are related to the ionic nature of these agents and their hyperosmolality, which may disrupt the electrolyte balance in the CSF and the central nervous system. The nonionic CM offer a class of agents characterized by the absence of ionic charge and reduced osmolality. Metrizamide **9** substantially increases patient safety and decreases both acute and chronic adverse reactions, but high cost and instability in solution are drawbacks to use. The second-generation water-soluble nonionic CM, iopamidol **10** and iohexol **11**, further decrease patient risk and offer lower cost and autoclaving stability. These last two agents are the approved and most widely used myelographic CM as of this writing (ca 1996).

An improved intrathecal radiographic agent should be nonionic, hydrophilic, and isoosmolar with CSF at the concentrations needed for radiography 78, 79. The development of nonionic demeric media is focused on further reducing osmolality, concomitantly lowering the neurotoxicity. A new series of candidates for myelographic agents is available. Iotrolan **31** 79, 80 and iodixanol **32** 81, available as of this writing in some European countries, are nonionic dimers that appear to possess higher neural tolerance and fewer side-effects in myelographic applications owing to the isotonic nature of these agents. Table 5 summarizes the important properties of these dimers. These compounds have six iodine atoms per molecule (ratio-6 CM) and exhibit the lowest osmolality of all water-soluble CM. On the other hand, they possess the highest viscosity, owing to large molecular sizes.

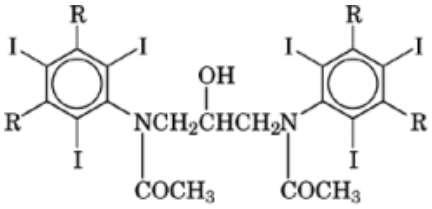
Table 5. Properties of Nonionic Dimeric Contrast Media[a]

Name								
Generic	Trade	Company name	Mol wt	Iodine content, %	Concentration[b] mg/mL	Osmolality, mOsm/kg H_2O	Viscosity, cps 20°C/37°C	LD_{50}[b], iv rats, g/kg
Iotrolan	Isovist	Schering AG	1626	46.8	240	270 82	6.8/3.9 (82)	26[c] (83)
					300	320 82	16.4/8.1 (82)	12.7 (83)
Iodixanol	Visipaque	Nycomed Imaging	1550	49.1	300	200 (81)	18.9/8.7 (81)	>21 (84)
					350	220 (81)		

[a] References cited are given in parentheses.
[b] Values given are on a weight of iodine basis.
[c] In mice.



(**31**) R = $CONHCH(CH_2OH)CH(OH)CH_2OH$



(**32**) R = $CONHCH_2CH(OH)CH_2OH$

3. Cholecystography and Cholangiography

Radiographic studies of the gallbladder and bile duct with radiopaques are called cholecystography and cholangiography, respectively 85, 86. Cholecystographic agents are administered orally for the evaluation of gallbladder abnormalities, such as gallstones. Cholangiographic agents are administered intravenously to produce opacification of the cystic and common bile ducts 85. Because of different biochemical transformations, oral cholecystographic agents and intravenous cholangiographic agents have distinct chemical requirements and pharmacokinetic properties.

3.1. Oral Agents

The orally administered media are absorbed through the gastrointestinal tract and, after entering the portal venous circulation, are taken up by the liver. Following hepatocyte uptake, the cholecystographic agents are metabolized (conjugated) to form their glucuronide derivatives and excreted through bile into the gallbladder. Therefore, cholecystographic agents require both hydrophilic and lipophilic properties. Hydrophilicity provides adequate water-solubility, necessary for initial dissolution of the CM in the bulk-water phase of the small intestine. Lipophilicity permits the diffusion of CM through the lipid membrane of the gastrointestinal

mucosa and influences the protein binding necessary for blood transport, liver uptake, and biliary excretion. Suitable oral cholecystographic CM are monomers of amino-triiodobenzene derivatives having alkanoic acid substituents (Table 6). Iopanoic acid [96-83-3] **33**, developed in the early 1950s, represents the first of a series of these oral biliary contrast media 88. Other commercially available agents include ipodoic acid [5587-89-3] **34** 89, iocetamic acid [16034-77-8] **35** 90 and tyropanoic acid [27293-82-9] **36** 91. These agents each contain an aliphatic carboxylic acid group capable of ionizing to form a water-soluble salt for increased solubility and intestinal absorption. Iopanoic acid is the least water-soluble agent of the group and has the highest albumin binding 92. The agents developed subsequently each display increased water solubility. In contrast to angiographic–urographic agents that contain substituents at the 1, 3, and 5 positions in the aromatic ring, position 5 is unsubstituted in cholecystographic agents. This structural feature plays an important role in imparting lipophilic binding with serum albumin and hence facilitating hepatobiliary vs renal excretion of the cholecystographic media.

Table 6. Chemical Structures and Solubilities of Cholecystographic Agents

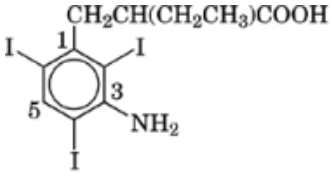
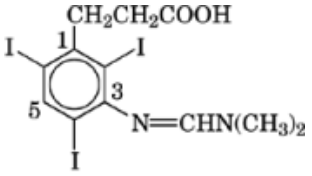
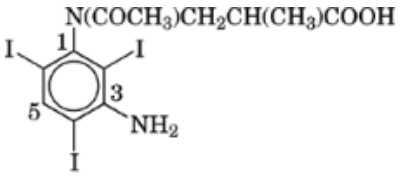
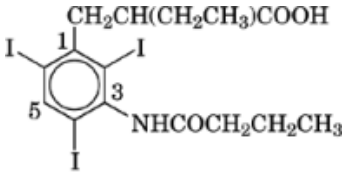
Name				
Generic	Trade	Company name	R R′	Aqueous solubility,[a] pH 7.4 and 37°C, mmol/L
iopanoic acid	Telepaque	Sterling-Winthrop Pharmaceuticals[b]	 **(33)**	0.61
ipodoic acid	Oragrafin	Squibb Diagnostics[c]	 **(34)**	1.87[d]
				3.75[e]

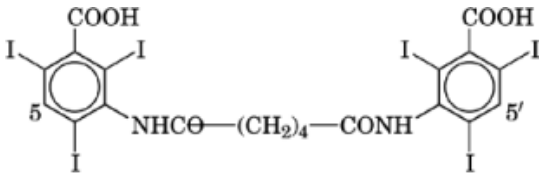
Table 6. ***Continued***

Name				
Generic	Trade	Company name	R R′	Aqueous solubility,[a] pH 7.4 and 37°C, mmol/L
iocetamic acid	Cholebrine	Mallinckrodt Medical	 **(35)**	8.61
tyropanoic acid	Bilopaque	Sterling-Winthrop Pharmaceuticals[b]	 **(36)**	26.48[e]

[a] Refs. 85 and 87.
[b] Nycomed Imaging, as of 1996.
[c] Bracco Diagnostics, as of 1996.
[d] Calcium salt.
[e] Sodium salt.

3.2. Intravenous Agents

Intravenous administration of biliary contrast agents circumvents the relatively slow absorption of the intestinal system 85 and allows for rapid and efficient heptocyte uptake and biliary excretion. Structurally, the intravenous biliary agents are dimers of triiodobenzene derivatives and differ only in the composition of the methylenic linkage. The relatively strong dibasic acid is ionized at physiological pH and, as a meglumine salt, is suitably soluble in water for intravenous administration. As for the oral agents, a high affinity for biliary excretion is based on the polar as well as lipophilic nature of the compounds, provided by the carboxylate groups and the unsubstituted 5 and 5′ positions on the dimers. Although it is not commercially readily available, the meglumine salt of iodipamide [606-17-7] **37** (Cholografin) 93, 94 is the only cholangiographic agent used in the United States. Ioglycamide [2618-25-9] **38** (Biligram) 93, 94 and iodoxamate [51764-33-1] **39** (Cholovue) 93, 95 were previously used in these applications.



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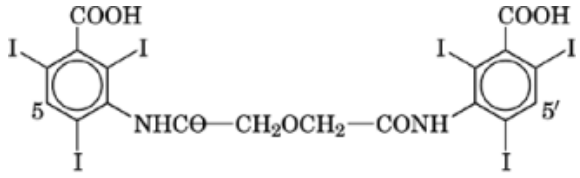

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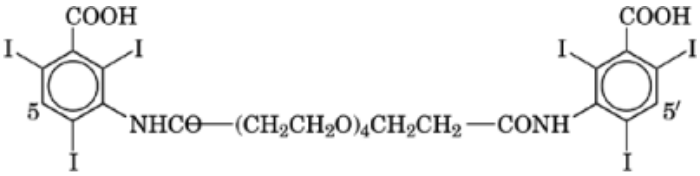


(39)

Although still valuable for selected studies, cholecystography and cholangiography have been largely replaced by other diagnostic modalities. Methologies include ultrasound, computed tomography, magnetic resonance, and radionuclide techniques see Magnetic spin resonance; Medical imaging technology; Radioactive elements.

4. Gastrointestinal Radiography

In the early development of radiopaques, barium sulfate [7727-43-7] was introduced for use in imaging the gastrointestinal (GI) tract 2, 96. This compound has remained the agent of choice for gastrointestinal radiography 97. Barium sulfate forms a colloidal suspension and is administered orally when the regions of interest reside in the upper GI tract, and rectally when the lower GI tract is the focus. Being chemically inert and practically insoluble in water, barium sulfate demonstrates negligible absorption from the digestive system and produces few physiological side effects. It is excreted in the feces unchanged.

Two types of imaging techniques are routinely used. Single-contrast imaging is performed using a large volume of low density barium sulfate preparation to fill the entire lumen of the GI segment, to produce full-column opacification. Double-contrast imaging utilizes a smaller amount of a high density, low viscosity barium preparation to coat the mucosal surface. Air or carbon dioxide, through the oral administration of commercially available sodium bicarbonate preparations for upper GI procedures, is then administered to distend the region and provide a negative contrast. In this way, surface detail of the GI tract is finely delineated.

Because the regions of the alimentary tract vary widely in pH and chemical composition, many different commercial formulations of barium sulfate are available. The final preparations of varying viscosity, density, and formulation stability levels are controlled by the different size, shape, uniformity and concentration of

barium sulfate particles and the presence of additives. The most important additives are suspending and dispersing agents used to maintain the suspension stability. Commercial preparations of barium sulfate include bulk and unit-dose powders and suspensions and principal manufacturers are E-Z-EM (Westbury, New York), Lafayette-Pharmacol, Inc. (Lafayette, Indiana), and Picker International, Inc. (Cleveland, Ohio).

Extravasation of barium sulfate into the peritoneal cavity through a perforated GI tract can produce serious adverse reactions. When a perforation is suspected, the use of a water-soluble iodinated contrast medium is indicated. In this case, oral or rectal administration of sodium or meglumine-sodium salts of diatrizoic acid **6** and oral use of iohexol **11** are the preferred procedures.

5. Computed Tomography

In computed tomography (CT) 98 the usual x-ray film image is replaced by sets of digitized matrices which represent the x-ray attenuation through the body. Multiple x-ray projections are utilized. After the data are computer-analyzed, cross-sectional views of the target organ(s) can be generated. The advantage of CT over the more conventional x-ray imaging technique is the greater contrast sensitivity to attenuation changes. However, because film is a continuous medium whereas the CT images are derived from digital picture elements (pixels), resolution of very small structures generated from a finite number of pixels can be limited using CT, as compared to conventional film-screen radiography.

The CT procedure can be performed with or without the use of intravenous contrast media. Contrast-enhanced CT involves the administration of a radiopaque to increase the degree of contrast between anatomical structures and to improve the differentiation between pathological and physiological phenomena. In general, because of the increased sensitivity of CT compared to film methods, lower concentrations of CM are indicated. The same water-soluble CM used in angiography and urography are successfully utilized to enhance contrast in CT (see Table 1). Because the CM reaches the various vessels and organs, eg, the brain, liver, and kidneys, at varying intervals, timing between CM administration and the collection of data is crucial. The CM gradually approaches equilibrium with body fluids and the resultant nonspecific opacification decreases the contrast sensitivity and curtails the clinically useful imaging time period.

In other applications of CT, orally administered barium sulfate or a water-soluble iodinated CM is used to opacify the GI tract. Xenon, atomic number 54, exhibits similar x-ray absorption properties to those of iodine. It rapidly diffuses across the blood brain barrier after inhalation to saturate different tissues of brain as a function of its lipid solubility. In preliminary investigations 99, xenon gas inhalation prior to brain CT has provided useful information for evaluations of local cerebral blood flow and cerebral tissue abnormalities. Xenon exhibits an anesthetic effect at high concentrations but otherwise is free of physiological effects because of its nonreactive nature.

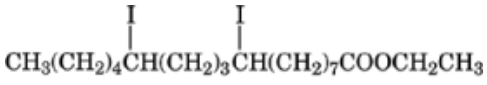
6. Arthrography

The radiological visualization of joint cavities using contrast media is termed arthrography 100. Single-contrast arthrographic techniques utilize direct injection of a water-soluble contrast agent that readily mixes with the synovial fluid, producing opacification of the joint surfaces and cavity. The CM is then rapidly absorbed and excreted in the urine. Double-contrast arthrography involves the removal of the joint fluid and injection of a water-soluble positive contrast agent to coat the surfaces of the joint, followed by the introduction of air or carbon dioxide as a negative contrast medium to fill the cavity. Double-contrast techniques can result in a finer delineation of surface contours than the single-contrast method, especially when combined with computed tomography. The water-soluble CM used in arthrography include meglumine diatrizoate **6**, meglumine iothalamate **7**, sodium and meglumine ioxaglate **18**, and iohexol **11**. Adverse physiological effects, such as pain

and swelling, are related to the hyperosmolality and chemical toxicity of the radiographic agent. The use of nonionic, ratio-3 LOCM minimizes these adverse effects 101.

7. Hysterosalpingography

Hysterosalpingography describes the radiological examination of the uterus and fallopian tubes for the purpose of detecting structural abnormalities and for the evaluation of fallopian tube patency. The CM for intrauterine administration include the oily agent Ethiodol, which consists of a mixture of ethyl esters of the iodinated fatty acids of poppy seed oil. The two main iodinated components of Ethiodol are diiodoethylstearate **40** and monoiodoethylstearate **41**. Iodipamide meglumine mixed with diatrizoate meglumine (Sinografin) is specifically indicated for the hysterosalpingographic procedure to provide adequate viscosity and proper retention of the agent. Other water-soluble agents include iohexol and meglumine-sodium salts of iothalamate, diatrizoate, and ioxaglate (see Table 1). Use of water-soluble agents eliminates the risk of adverse effects, such as granulomas and pulmonary embolism, resulting from prolonged retention of an oily agent 102.



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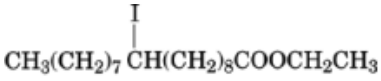

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8. Contrast Media Under Development

The continuing search for new radiopaque agents possessing desirable properties promises to benefit many aspects of diagnostic medicine. Permutations in the side-chain substituents affect the physicochemical and biological properties of the triiodobenzene CM. The presence of a primary carboxamide substituent, $-CONH_2$, enhances water solubility because of its polarity, whereas its small size does not interfere with intermolecular hydrophobic interactions. Hydrophobic bonding between molecules may produce aggregation of the CM in solution, thereby lowering the osmolality 103, 104. Some heterocyclic substituents may confer an anticoagulant property which is desirable in a nonionic CM for angiographic applications 105, 106. Water-insoluble particulate CM, derived from esters of metrizoic acid and iodipamide, have potential for contrast-enhanced CT scanning of the liver 107, 108. In animal experiments, contrast-carrying liposomes using several CM have been demonstrated to be taken up by the reticuloendothelial system, thus functioning as imaging agents for the liver and spleen 109–115. Iodinated polymers having increased molecular weights that keep the material trapped in the vascular space longer are being investigated as blood-pool agents 116–119. Perfluorooctylbromide [423-55-2] (perflubron), $C_8F_{17}Br$, wherein bromine is the radiopaque element 98, 120, has also been studied for blood-pool applications as well as for lymph node imaging using CT 121, 122.

Other imaging techniques such as magnetic resonance and ultrasound have opened up avenues of tremendous potential for contrast medium enhancement 123. Ultrasound contrast media developments have centered around encapsulated air micro-bubbles. Magnetic resonance contrast agents involve metal–ligand complexes and have evolved from ionic to nonionic species, much as radiopaques have.

Radiopaques, including LOCM, HOCM, and barium sulfate, accounted for $\$3.32 \times 10^9$ in world revenue and $\$1.22 \times 10^9$ in U.S. revenue 124.

BIBLIOGRAPHY

"Radiopaques" in *ECT* 2nd ed., Vol. 17, pp. 130–142, by James Ackerman, Sterling-Winthrop Research Institute; in *ECT* 3rd ed., Vol. 19, pp. 786–801, by J. Ackerman, Sterling-Winthrop Research Institute.

Cited Publications

1. *International Tables for X-ray Crystallography*, Vol. **III**, Kynoch Press, Birmingham, U.K., 1974, pp. 161 ff; distributed by Kluwer Academic Publishers, Dordrecht, the Netherlands.
2. W. H. Strain, in P. K. Knoefel, ed., *International Encyclopedia of Pharmacology and Therapeutics*, Sect. 76, Vol. **1**, Pergamon Press, Oxford, U.K., 1971, Chapt. 1, 1–22, for a review of the historical development of radiopaques.
3. M. Swick, *J. Am. Med. Assoc.* **95**, 1403 (1930).
4. H. L. Abrams, *Abrams Angiography: Vascular and Interventional Radiology*, 3rd ed., Vol. **1**, Little, Brown and Co., Boston, Mass., 1983, 3–14.
5. R. G. Grainger, *Br. J. Radiol.* **55**, 1 (1982).
6. J. O. Hoppe, A. A. Larsen, and F. Coulston, *J. Pharmacol. Exptl. Therap.* **166**, 394 (1956).
7. A. von Lichtenberg, *Br. J. Urol.* **3**, 119 (1931).
8. V. H. Wallingford, *J. Am. Pharmacol. Assoc.* **42**, 721 (1953).
9. V. H. Wallingford, H. G. Decker, and M. Kruty, *J. Am. Chem. Soc.* **74**, 4365 (1952).
10. G. B. Hoey and K. R. Smith, in M. Sovak, ed., *Radiocontrast Agents*, Springer-Verlag, New York, 1984, 23–125.
11. G. B. Hoey, P. E. Wiegert, and R. D. Rands, in Ref. 2, Chapt. 2, 23–131.
12. D. P. Swanson, P. C. Shetty, D. J. Kastan, and N. Rollins, in D. P. Swanson, H. M. Chilton, and J. H. Thrall, eds., *Pharmaceuticals in Medical Imaging*, Macmillan Co., New York, 1990, Chapt. 1, 1–77.
13. H. W. Fischer, *Radiol.* **159**, 561 1986.
14. J. O. Hoppe, L. P. Duprey, W. A. Borisenok, and J. G. Bird, *Angiography* **18**, 257 (1967).
15. G. B. Hoey, R. D. Rands, G. B. DeLaMater, D. W. Chapman, and P. E. Wiegert, *J. Med. Chem.* **6**, 24 (1963).
16. Technical data, Mallinckrodt Medical Inc., St. Louis, Mo., 1989.
17. B. L. McClennan, *Am. J. Roentgenol* **155**, 225 (1990).
18. R. F. Spataro, *Radiol. Clin. North Am.* **22**, 365 (1984).
19. B. L. McClennan, *Radiology* **162**, 1 (1987).
20. P. Dawson, *Invest. Radiology* **19**, S293 (1984).
21. H. W. Fischer, R. F. Spataro, and P. M. Rosenberg, *Arch. Intern. Med.* **146**, 1717 (1986).
22. T. AlmÉn, *J. Theor. Biol.* **24**, 216 (1969).
23. T. AlmÉn, *Invest. Radiol.* **15**(suppl), S283 (1980).
24. E. C. Lasser, J. H. Lang, A. E. Hamblin, S. G. Lyon, and M. Howard, *Invest. Radiol.* **15**(suppl), S2 (1980).
25. T. S. Padayachee, J. F. Reidy, D. H. King, M. Reeves, and R. G. Gosling, *Clin. Radiol.* **34**, 79 (1983).
26. *Invest. Radiol.* **19**(suppl), S164–S285 (1984).
27. *Ibid.* pp. S289–S392.
28. *Invest. Radiol.* **20**(suppl), S2–S121 (1985).
29. *Invest. Radiol.* **24**(suppl), S1–S76 (1989).
30. J. C. Holder and G. V. Dalrymple, *Invest. Radiol.* **16**, 508 (1981).
31. I. J. Gordon and J. L. Wescott, *Radiology* **124**, 43 (1977).
32. T. Almén, *Invest. Radiology* **20**(suppl), S2 (1985).
33. Ger. Offen 2,031,724 (Jan. 7, 1971), T. Almén, J. Haavaldsen, and V. Nodal (to Nyegaard & Co.).
34. Ger. Offen 2,547,789 (Jan. 24, 1976), E. Felder and D. E. Pitrè (to Savac AG).
35. U.S. Pat. 4,001,323 (Jan. 4, 1977), E. Felder, R. S. Vitale, and D. E. Pitrè (to Savac AG).

36. E. Felder, M. Grandi, D. Pitrè, and G. Vittadini, in K. Florey, ed., *Analytical Profiles of Drug Substances*, Vol. **17**, Academic Press, Inc., New York, 1988, 115–154.
37. T. K. Kawada, *Drug Intell. Clin. Phar.* **19**, 525 (1985).
38. Ger. Offen 2,726,196 (June 10, 1977), V. Nordal and H. Holtermann.
39. Brit. Pat. 1,548,594 (June 11, 1976), V. Nordal and H. Holtermann.
40. U.S. Pat. 4,250,113 (Feb. 10, 1981), V. Nordal and H. Holtermann.
41. U.S. Pat. 4,396,598 (Aug. 2, 1983), Y. Lin.
42. U.S. Pat. 4,352,788 (Oct. 5, 1982), E. Felder, R. S. Vitale, and D. Pitrè (to Bracco Industria Chimica).
43. M. Sovak, in Z. Parvez, ed., *Contrast Media: Biologic Effects and Clinical Applications*, Vol. **1**, CRC Press, Boca Raton, Fla., 1987, 27–45.
44. Technical data, Squibb Diagnostics, Princeton, N.J., 1993.
45. J. Haavaldsen, V. Nordal, and M. Kelly, *Acta Pharm. Suec.* **20**, 219 (1983).
46. Technical data, Sanofi-Winthrop, New York, 1993.
47. B. Bonnemain, personal communication, Guerbet Laboratory, Aulnay-sous-Bois, France, Nov. 1994.
48. W. H. Ralston, M. S. Robbins, J. Coveney, and M. Blair, *Invest. Radiol.* **24**(suppl), S2 (1989).
49. Technical data, Mallinckrodt Medical Inc., St. Louis, Mo., 1994.
50. S. P. H. Eggleton and E. Puchert, *X-Ray Contrast Media Made Clear*, Schering AG, Germany, 1992.
51. Eur. Pat. Appl. 105,752 A1 (Apr. 18, 1984), K. Wille (to Nyegaard & Co.).
52. K. Skinnemoen, *Acta Radiol.* **370**(suppl), 33 (1987).
53. U.S. Pat. 4,954,348 (Sept. 4, 1990), M. Sovak and R. Ranganathan.
54. Technical data, Mallinckrodt Medical Inc., St. Louis, Mo., 1988.
55. U.S. Pats. 3,701,771 (Oct. 31, 1972) and 4,021,481 (May 3, 1977), T. Almén, J. Haavaldsen, and V. Nordal.
56. M. D. Adams, W. H. Ralston, J. W. Miller, and J. A. Ferrendelli, *Proceedings of the Second International Symposium on Contrast Media*, Osaka, Japan, Nov. 9–10, 1990; *Excerpta Medica*, 17–23 (1991); M. D. Adams, W. H. Ralston, J. W. Miller, and J. A. Ferrendelli, *Invest. Radiol.* **25**(suppl), S86 (1990).
57. W. Mützel and U. Speck, *Fortschr. Geb. Röntgenstr. Nuklearmed. Ergänzungsbd.* **118**, 11 (1983).
58. B. Bonnemain and co-workers, *Invest. Radiol.* **25**(suppl), S104 (1990).
59. A. Morisetti, P. Tirone, F. Luzzani, and C. de Haën, *Eur. J. Radiol.* **18**(suppl), S21 (1994).
60. M. Sovak, *Invest. Radiol.* **23**(suppl), S79 (1988).
61. J. H. Wible, Jr., S. J. Barco, D. E. Scherrer, J. K. Wojdyla, and M. D. Adams, *Eur. J. Radiol.* **19**, 206–211 (1995).
62. A. A. Michelet, S. Salvesen, and T. Renaa, *Acta Radiol.* **370**(suppl), 41 (1987).
63. R. W. Katzberg and co-workers, *Invest. Radiol.* **25**, 46 (1990).
64. R. F. Spataro, *Urol. Radiol.* **10**, 2 (1988).
65. B. F. King, G. W. Hartman, B. Williamson, A. J. LeRoy, and R. R. Hattery, *Mayo Clin. Proc.* **64**, 976 (1989).
66. H. Katayama and co-workers, *Radiology* **175**, 621 (1990).
67. T. Almén, *Invest Radiol.* **29**(suppl), S37 (1994).
68. P. K. Knoefel, in Ref. 2, Chapt. 3, 131–145.
69. H. Levitan and S. I. Rapoport, *Acta Radiol. Diagn.* **17**, 81 1976.
70. T. Almén, *Am. J. Cardiol.* **66**, 2F 1990.
71. W. Krause, *Invest. Radiol.* **29**(suppl), S21–S32 (1994), and other articles in this supplement, pp. S68–S117.
72. Eur. Pat. Appl. 437,144 A1 (Dec. 26, 1990), M. Schaefer, M. Dugat-Zrihen, M. Guillemot, D. Doucet, and D. Meyer (to Guerbet SA).
73. U.S. Pat. 4,065,554 (Dec. 27, 1977), G. Tilly, M. J. C. Hardouin, and J. Lautrou (to Guerbet Laboratories).
74. P. Blaszkiewicz, *Invest. Radiol.* **29**(suppl), S51 (1994).
75. D. R. Dakins, *Diag. Imag.*, 43 (Feb. 1991).
76. D. P. Swanson and R. S. Boulos, in Ref. 12, Chapt. 4, 125–154, and references therein.
77. G. B. Hoey and co-workers, *J. Med. Chem.* **9**, 964 1966.
78. M. Sovak, *Invest. Radiol.* **19**suppl, S134 (1984).
79. M. Sovak, R. Ranganathan, and B. Hammer, *Invest. Radiol.* **19**(suppl), S139 (1984).
80. U.S. Pat. 4,341,756 (July 27, 1982), M. Sovak and R. Ranganathan (to University of California).
81. Eur. Pat. Appl. 108,638 A1 (May 16, 1984), P-E. Hanson, H. Holtermann, and K. Wille (to Nyegaard & Co.); Eur. Pat. 108,638 B1 (July 7, 1986).

82. *Isovist™ technical brochure*, Schering Health Care, West Sussex, U.K.
83. M. Sovak, R. Ranganathan, and U. Speck, *Radiology* **142**, 115 (1982).
84. J. O. Nossen, T. Aakhus, K. J. Berg, N. P. Jorgensen, and E. Andrew, *Invest. Radiol.* **25**(suppl), S113 (1990).
85. D. P. Swanson and S. M. Simms, in Ref. 12, Chapt. 6, 184–220.
86. V. G. Urich and U. Speck, *Progr. Pharm. Clin. Pharm.* **8**, 307 1991.
87. J. O. Janes, J. M. Dietschy, R. N. Berk, P. M. Loeb, and J. L. Barnhart, *Gastroenterology* **76**, 970 1979.
88. T. R. Lewis and S. Archer, *J. Am. Chem. Soc.* **71**, 3753 (1949).
89. H. Priewe and A. Poljak, *Chem. Ber.* **93**, 2347 (1960).
90. J. A. Korver, *Rec. Trav. Chim. Pays-Bas* **87**, 308 (1968).
91. J. O. Hoppe, J. H. Ackerman, A. A. Larsen, and J. Moss, *J. Med. Chem.* **13**, 997 (1970).
92. J. H. Lang and E. C. Lasser, *Invest. Radiol.* **2**, 396 (1967).
93. J. L. Barnhart, in Ref. 10, 367–418.
94. H. Priewe, R. Rutkowski, K. Pirner, and K. Junkmann, *Chem. Ber.* **87**, 651 1954.
95. E. Felder, D. Pitrè, L. Fumagalli, and E. Lorenzotti, *Farmaco Ed. Sci.* **28**, 912 1973.
96. C. Bachem and H. Gunther, *Z. Rontgenk. Rad. Forschr.* **12**, 369 (1910).
97. D. P. Swanson and R. D. Halpert, in Ref. 12, Chapt. 5, 155–183.
98. D. P. Swanson and M. B. Alpern, in Ref. 12, Chapt. 3, 99–124.
99. J. S. Meyer, L. A. Hayman, M. Yamamoto, F. Sakai, and S. Nakajima, *Am. J. Roentgenol.* **135**, 239 1980.
100. D. P. Swanson and B. I. Ellis, in Ref. 12, Chapt. 7, 221–252.
101. F. M. Hall, D. I. Rosenthal, R. P. Goldberg, and G. Wyshak, *Am. J. Roentgenol.* **136**, 59 1981.
102. H. Y. Yune, in R. E. Miller and J. Skucas, eds., *Radiographic Contrast Agents*, University Park Press, Baltimore, Md., 1977, 307–321.
103. M. Sovak, R. C. Terry, J. G. Douglass, and L. Schweitzer, *Invest. Radiol.* **26**(suppl), S159 (1991).
104. Eur. Pat. Appl. 406,992 A2 (June 29, 1990), M. Sovak (to Schering Aktiengesellschaft).
105. Eur. Pat. Appl. 431,838 A1 (Nov. 29, 1990), R. S. Ranganathan, E. R. Marinelli, T. Arunachalam, and R. Pillai (to Squibb & Sons).
106. Eur. Pat. Appl. 516,050 A2 (May 26, 1992), R. S. Ranganathan, P. W. Wedeking, M. F. Tweedle, and R. Pillai (to Squibb & Sons).
107. M. S. Sands, M. R. Violante, and G. Gadeholt, *Invest. Radiol.* **22**, 408 (1987).
108. P. Leander and co-workers, *Invest. Radiol.* **28**, 513 (1993).
109. S. E. Seltzer, *Invest. Radiol.* **23**(suppl), S122 (1988).
110. D. Revel and co-workers, *Invest. Radiol.* **25**(suppl), S95 (1990).
111. T. Gjoen and co-workers, *Invest. Radiol.* **25**(suppl), S98 (1990).
112. R. Passariello and co-workers, *Invest. Radiol.* **25**(suppl), S92 (1990).
113. A. S. Janoff and co-workers, *Invest. Radiol.* **26**(suppl), S167 (1991).
114. S. E. Seltzer and co-workers, *Invest. Radiol.* **26**(suppl), S169 (1991).
115. W. Krause, A. Sachse, S. Wagner, U. Kollenkirchen, and G. Rössling, *Invest. Radiol.* **26**(suppl), S172 (1991).
116. Int. Pat. Appl. WO 88/06162 (Aug. 25, 1988), D. Paris, J-M. Nigretto, B. Bonnemain, D. Meyer, and D. Doucet.
117. D. Doucet, D. Meyer, C. Chambon, and B. Bonnemain, *Invest. Radiol.* **26**(suppl), S53 (1991).
118. D. Revel and co-workers, *Invest. Radiol.* **26**(suppl), S57 (1991).
119. J. Lautrou and co-workers, *Invest. Radiol.* **25**(suppl), S109 (1990).
120. D. M. Long, E. C. Lasser, C. M. Sharts, F. K. Multer, and M. Nielsen, *Invest. Radiol.* **15**, 242 (1980).
121. R. F. Mattrey, *Invest. Radiol.* **26**(suppl), S55 (1991).
122. G. Hanna and co-workers, *Invest. Radiol.* **29**(suppl), S33 (1994).
123. D. D. Shaw, *Invest. Radiol.* **28**(suppl), S138 (1993).
124. Frost and Sullivan, *World Contrast Media Market, New Dynamics in an Evolving Market*, Mallinkrodt Medical, St. Louis, Mo., 1994.

General References

125. J. Ackerman, *Diagnostic Agents*, in A. Burger, ed., *Medicinal Chemistry*, 3rd ed., Part II, John Wiley & Sons, Inc., New York, 1970, Chapt. 67, 1686–1699.
126. P. K. Knoefel, ed., *International Encyclopedia of Pharmacology and Therapeutics*, Sect. 76, Pergamon Press, Oxford, U.K., 1971.
127. Z. Parvez, ed., *Contrast Media: Biologic Effects and Clinical Applications*, **3** vols., CRC Press, Boca Raton, Fla., 1987.
128. M. Sovak, ed., *Radiocontrast Agents*, Springer-Verlag, New York, 1984.
129. M. Sovak, in M. Sovak, ed., *Handbook of Experimental Pharmacology*, Vol. **73**, Springer-Verlag, New York, 1984.
130. D. P. Swanson, H. M. Chilton, and J. H. Thrall, eds., *Pharmaceuticals in Medical Imaging*, Macmillan Co., New York, 1990.

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