



Office de la Propriété
Intellectuelle
du Canada

Un organisme
d'Industrie Canada

Canadian
Intellectual Property
Office

An agency of
Industry Canada

CA 2068089 C 2003/09/16

(11)(21) **2 068 089**

(12) **BREVET CANADIEN
CANADIAN PATENT**

(13) **C**

(22) **Date de dépôt/Filing Date:** 1992/05/06
(41) **Mise à la disp. pub./Open to Public Insp.:** 1992/12/01
(45) **Date de délivrance/Issue Date:** 2003/09/16
(30) **Priorité/Priority:** 1991/05/31 (708,656) US

(51) **Cl.Int.⁵/Int.Cl.⁵** C07D 307/30, A61K 49/04,
C07D 405/12, C07D 211/72, C07D 333/36,
C07D 309/28, C07D 207/22
(72) **Inventeurs/Inventors:**
RANGANATHAN, RAMACHANDRAN S., US;
TWEEDLE, MICHAEL F., US;
WEDEKING, PAUL W., US;
PILLAI, RADHAKRISHNA, US
(73) **Propriétaire/Owner:**
BRACCO IMAGING S.P.A., IT
(74) **Agent:** OSLER, HOSKIN & HARCOURT LLP

(54) **Titre : METHODE ET COMPOSITIONS POUR L'UTILISATION D'AGENTS DE CONTRASTE NON IONIQUES
REDUISANT LE RISQUE DE FORMATION DE CAILLOTS DANS LES METHODES DIAGNOSTIQUES**
(54) **Title: METHOD AND COMPOSITIONS FOR USING NON-IONIC CONTRAST AGENTS TO REDUCE THE RISK OF
CLOT FORMULATION IN DIAGNOSTIC PROCEDURES**

(57) **Abrégé/Abstract:**

In accordance with the present invention a novel method and composition for using nonionic contrast media to reduce the risk of clot formation in a diagnostic procedure is disclosed. Novel compositions for such method are also disclosed. The present method comprises employing a triiodinated phenyl contrast agent having a heterocyclic group or a dimeric triiodinated phenyl contrast agent having one or more heterocyclic groups.



ABSTRACT OF THE DISCLOSUREMETHODS AND COMPOSITIONS FOR USING NON-IONIC
CONTRAST AGENTS TO REDUCE THE RISK OF
CLOT FORMATION IN DIAGNOSTIC PROCEDURES

In accordance with the present invention a novel method and composition for using nonionic contrast media to reduce the risk of clot formation in a diagnostic procedure is disclosed. Novel compositions for such method are also disclosed. The present method comprises employing a triiodinated phenyl contrast agent having a heterocyclic group or a dimeric triiodinated phenyl contrast agent having one or more heterocyclic groups.

METHODS AND COMPOSITIONS FOR USING NON-IONIC
CONTRAST AGENTS TO REDUCE THE RISK OF
CLOT FORMATION IN DIAGNOSTIC PROCEDURES

- 5 Non-ionic contrast media, e.g. iopamidol
and iohexol, for use in angiography, have enjoyed
wide-spread acceptance in the diagnostic field in
recent years. The primary reasons for this
revolve around the fact that the frequency of
10 adverse reactions to intravenous injection
of non-ionic contrast media, compared with most
ionic contrast media (e.g., diatrizoate, sodium
meglumine and the like) is reduced by a factor of
two.
- 15 In a limited number of cases, however,
clotting has been observed during administration
of the angiographic procedure utilizing non-ionic
agents. Investigations into this infrequent, but
disturbing, phenomenon have unanimously confirmed
20 that the contrast media themselves, whether ionic
or non-ionic, are not actively thrombogenic.
Several *in vitro* studies agree that the ionic
contrast media typically have greater anticoagulant

effects as compared to their non-ionic counterparts. Careful selection of any appropriate contrast medium for angiographic procedures therefore involves a consideration of, among other factors, the inherent lower chemotoxicity of the non-ionics balanced against the greater anticoagulant effects of the ionics.

Researchers now believe this rare clotting phenomenon to be the result of the procedure employed by the practitioner. Apparently, in cases where aspirated blood is allowed to stand in the contrast material syringe, i.e. in contact with the non-ionic agent, for several minutes prior to the procedure, thrombus formation is possible. Various modifications and improvements to technique are considered to be the primary solution to this limited problem. Nevertheless, another measure to safeguard against this potential technique-induced clotting has been the utilization of anticoagulant agents. This measure is also called for in subjects who are otherwise prone to thrombus formation.

One widely used agent known for its anticoagulant activity is heparin. It is generally believed that the angiographic procedure does not warrant systemic heparin administration, although systemic heparin administration has been used, especially in subjects with histories of hyper-aggregation. Combinations of heparin and the contrast media have been tried in these types of procedures. This has not been without difficulties, however. Considering the naturally competing processes of coagulation and fibrinolysis and the

problems which an imbalance in either direction may cause, that is, thromboses or hemorrhage, respectively, it is generally understood that employment of heparin is not without risks.

5 Further, it is believed that some cases of cardiac ischaemia and ischaemic brain injury may be the result of heparinisation during angiography.

European Patent Application 0 390 242 teaches that the red blood cell aggregation in
10 human blood can be reduced by the addition of sodium chloride to nonionic contrast medium at a concentration of 20-60 mM. This approach, however, has the undesirable effect of increasing the osmolality of the non-ionic contrast medium.

15 Improved compositions and methods for using non-ionic contrast media in either angiographic procedures or patients where enhanced potential for thrombus formation exists would be a useful addition to the art.

20 In accordance with the present invention a novel method and composition for using nonionic contrast media to reduce the risk of clot formation in a diagnostic procedure is disclosed. Novel compounds for such method are also
25 disclosed. The present method comprises employing a triiodinated phenyl contrast agent having a heterocyclic group or a dimeric triiodinated phenyl contrast agent having one or more heterocyclic groups.

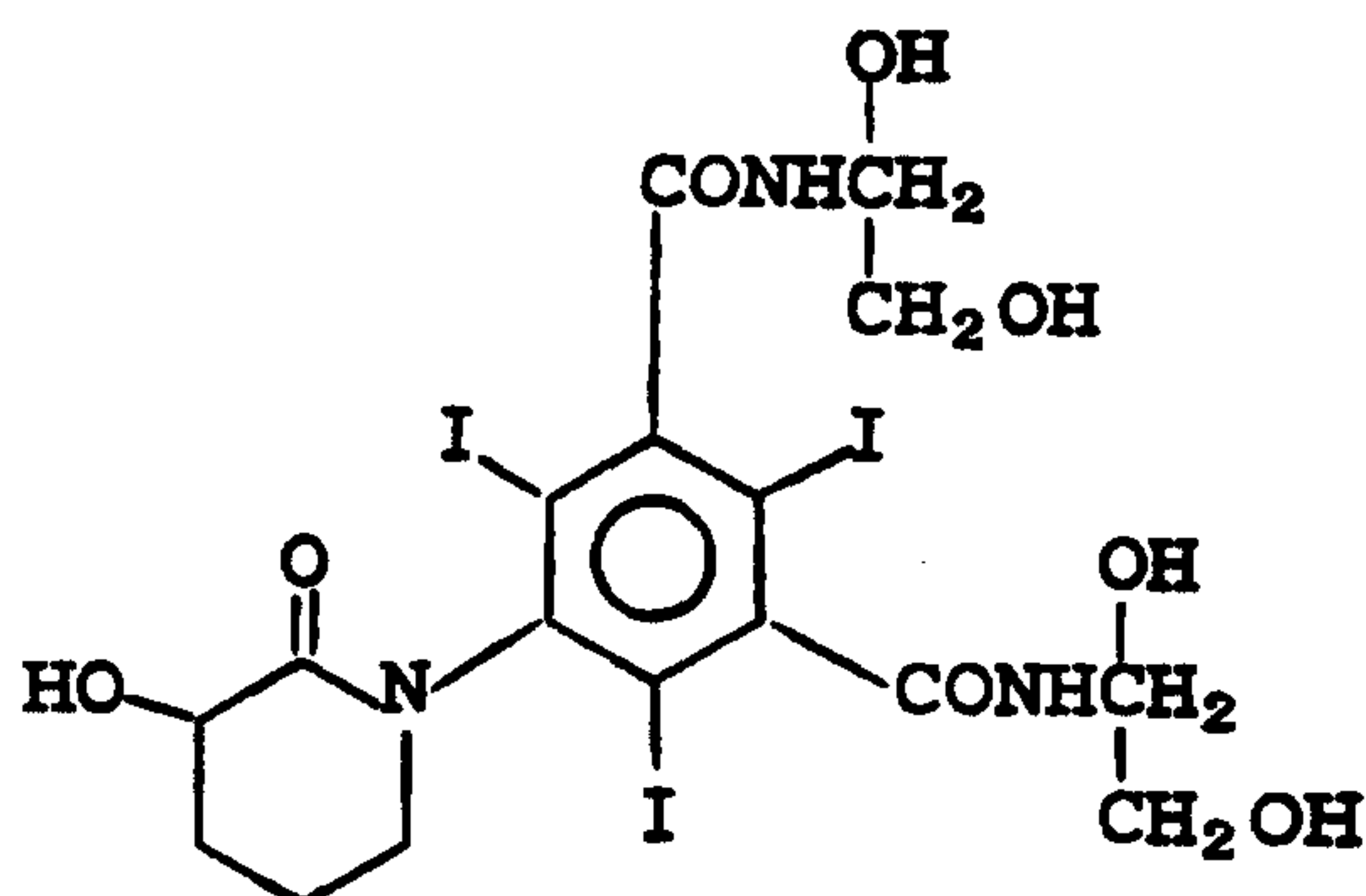
RA58

-4-

In its broadest aspects the present invention pertains to methods and compositions using nonionic contrast media to reduce the risk of clot formation in circumstances where the potential for clot formation exists. As described above, such risks may be the result of the particular angiographic procedure or technique employed or may be inherent in the patient to be subjected to the diagnostic procedure. An unexpected degree of anticoagulant behavior has been observed in the compound

15

20

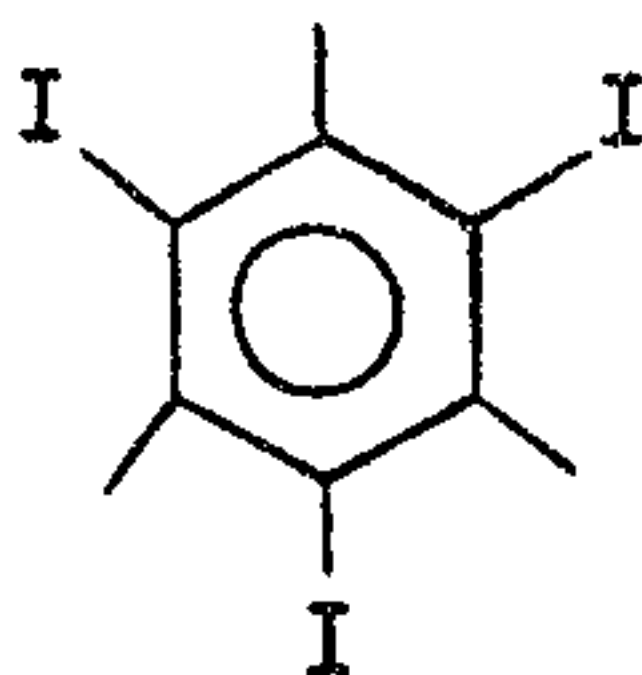


It has now been found that the class of triiodinated phenyl compounds having an unsubstituted or appropriately substituted heterocyclic group, or dimeric forms thereof having one or more heterocyclic groups, have properties indicating anti-coagulant behavior greater than that of nonionic agents lacking such heterocyclic substitution. In

30

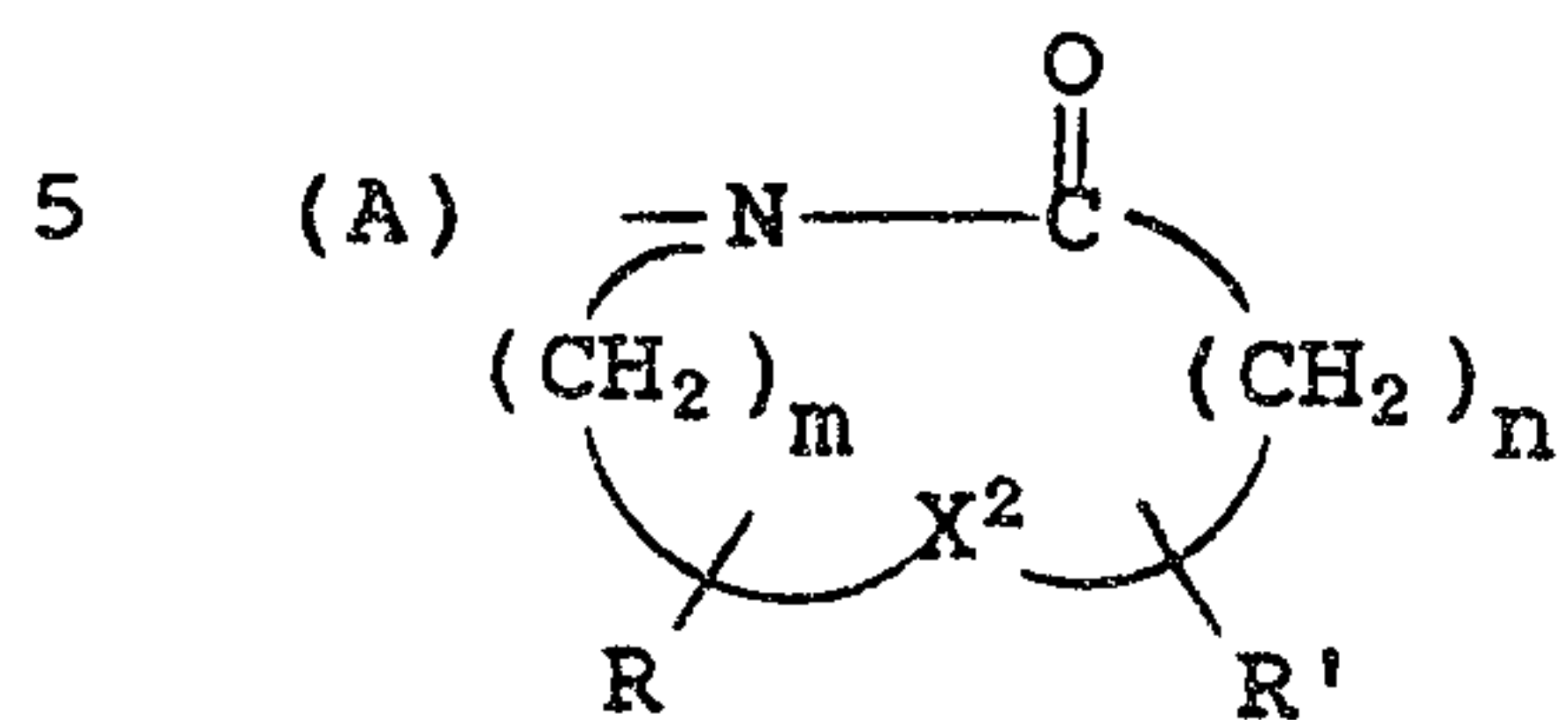
some cases the anticoagulant activity is equal to or greater than that of ionic contrast agents. This is believed to provide an enhanced measure of safety for all diagnostic procedures, especially those wherein the potential for clot formation is thought to be a problem. Thus, the present methods and compositions have the advantage of less side effects as compared to using ionic agents, but with anticoagulant properties greater than those of other non-ionic agents and anti-coagulant properties equal to or greater than those of the ionic agents.

The nonionic contrast agents having anticoagulant properties which are useful in the present methods and compositions include a triiodinated phenyl nucleus

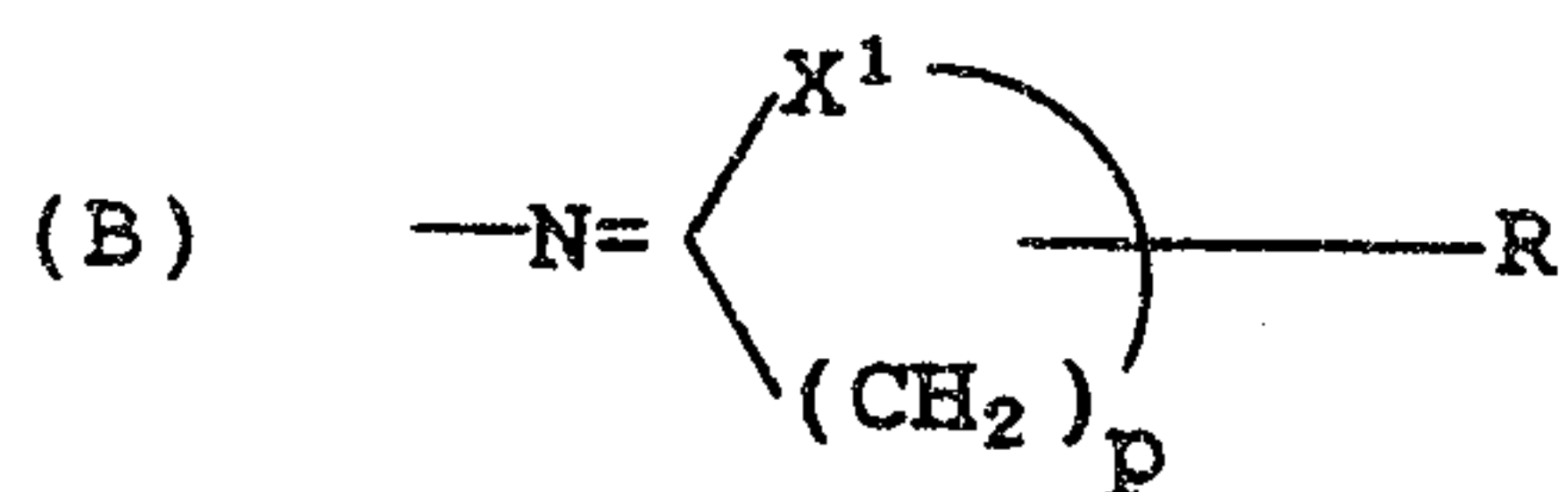


which has a heterocyclic substituent at one or more than one of the positions not substituted with iodine. Preferred are those compounds having 4-6 hydroxy groups and most preferred are those having 5 hydroxy groups. Especially preferred are those compounds having most of the hydroxy groups at positions remote to the heterocyclic group(s). For example, compounds having 1 or 2 hydroxy groups on the heterocyclic moiety and 3 or 4 of its hydroxy groups at R_1 and R_2 in formula I below, are believed to be more stable and less toxic.

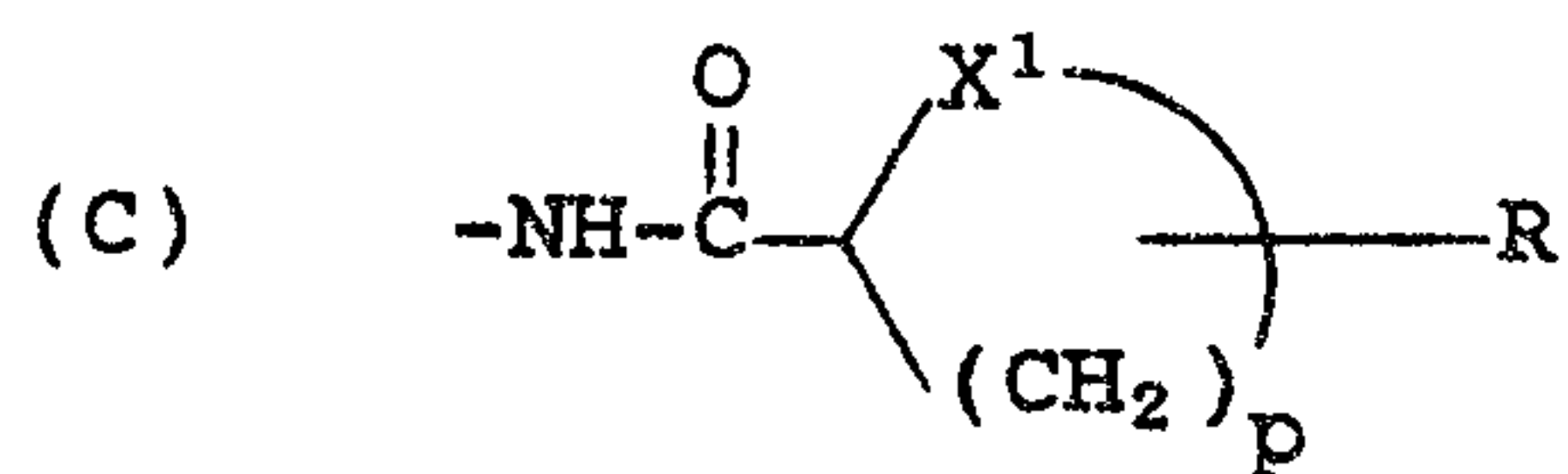
The heterocyclic group or groups are preferably selected from



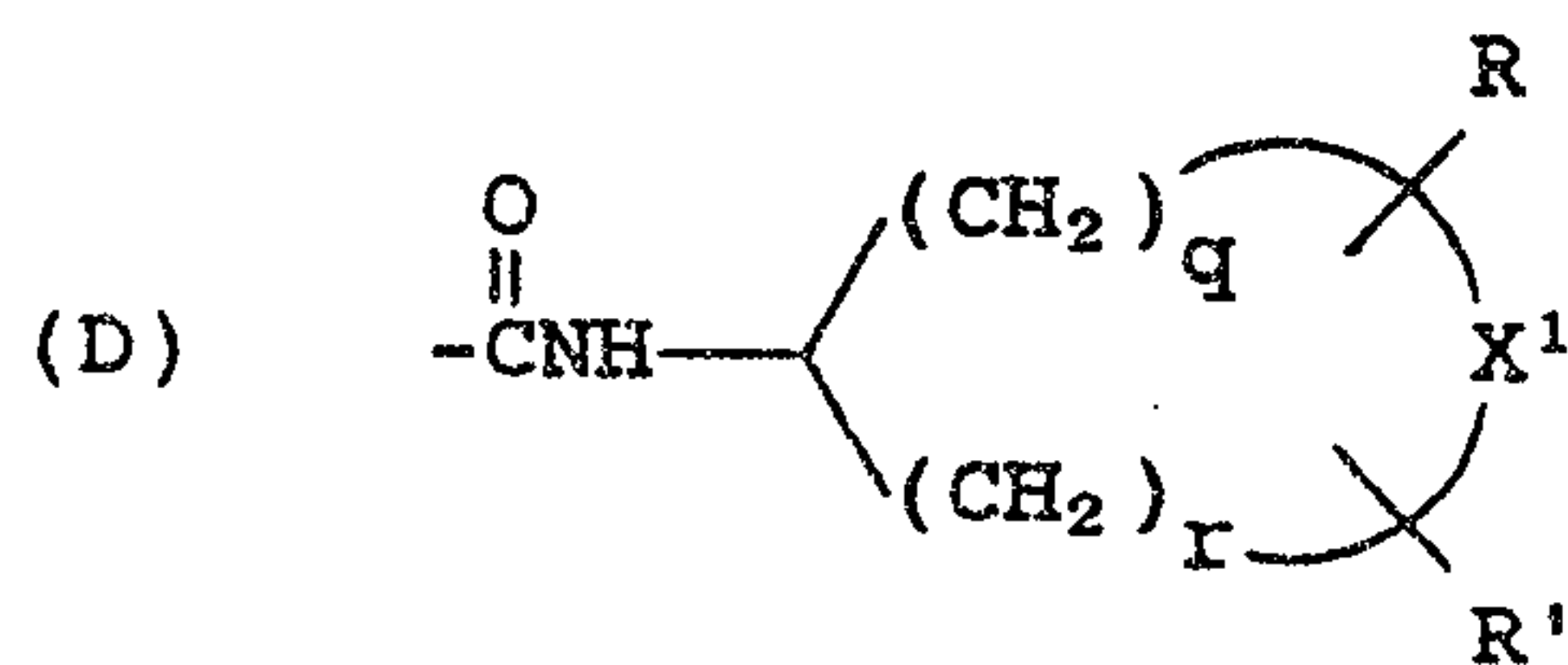
10



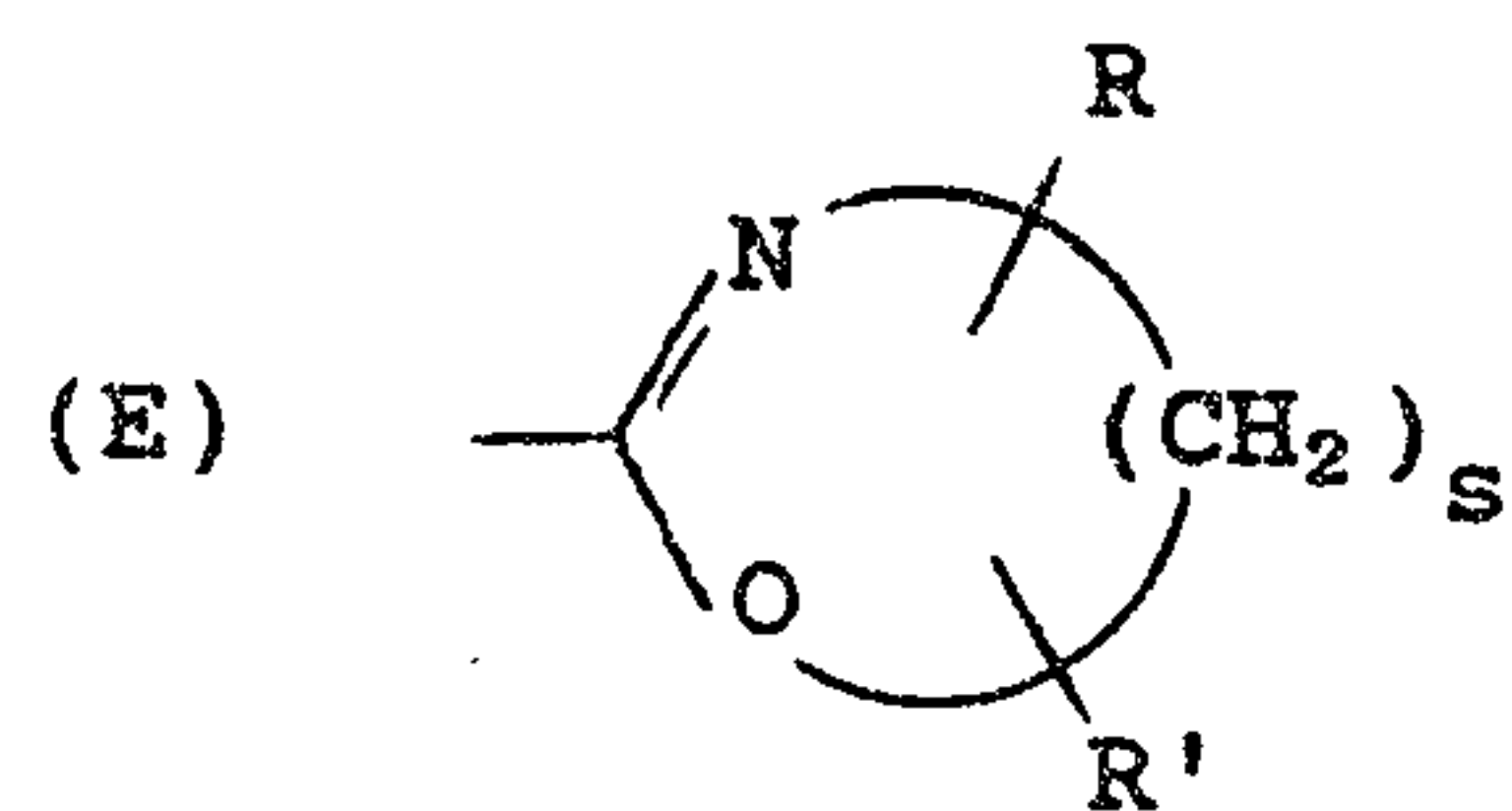
15



20



25



30

wherein R and R' are independently selected from hydrogen, alkyl, hydroxy, alkoxy, hydroxyalkyl and alkoxyalkyl;

5 X^1 is $\begin{array}{c} \text{O} \\ \parallel \\ \text{N}-\text{CH} \\ | \end{array}$, $\begin{array}{c} \text{O} \\ \parallel \\ \text{N}-\text{Calkyl} \\ | \end{array}$, -S- or -O-;

X^2 is X^1 or $-\text{CH}_2-$;

m is 1-4 or if X^2 is $-\text{CH}_2-$, m is 0-4;

n is 0-3;

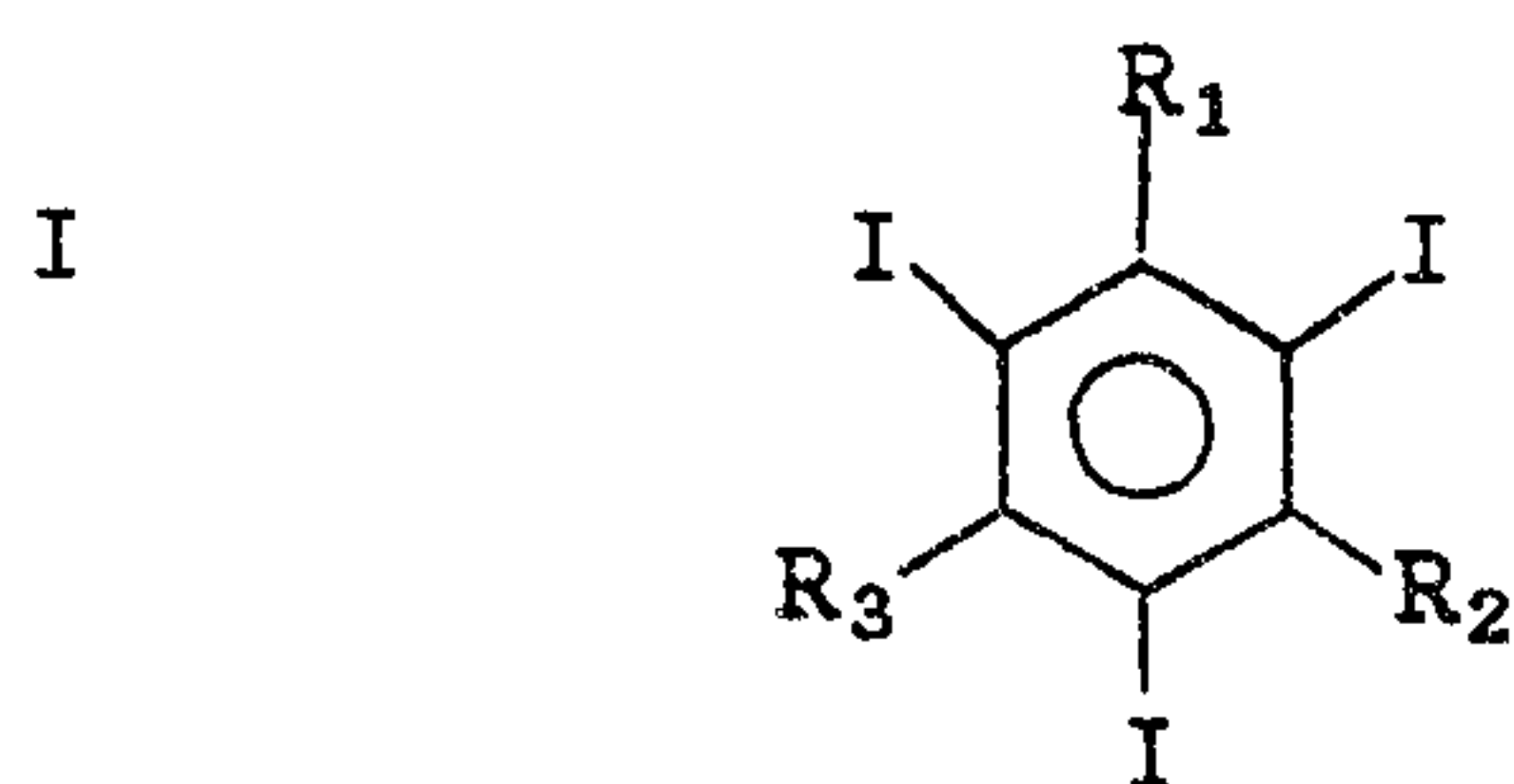
10 p is 2-5;

q and r are independently 1 or 2; and

s is 2-5.

Preferably the triiodinated phenyl contrast agent is of the formula

15



20

wherein R_1 is $\begin{array}{c} \text{O} \text{ } R_4 \\ \parallel \quad | \\ -\text{C}-\text{N}-R_6 \end{array}$;

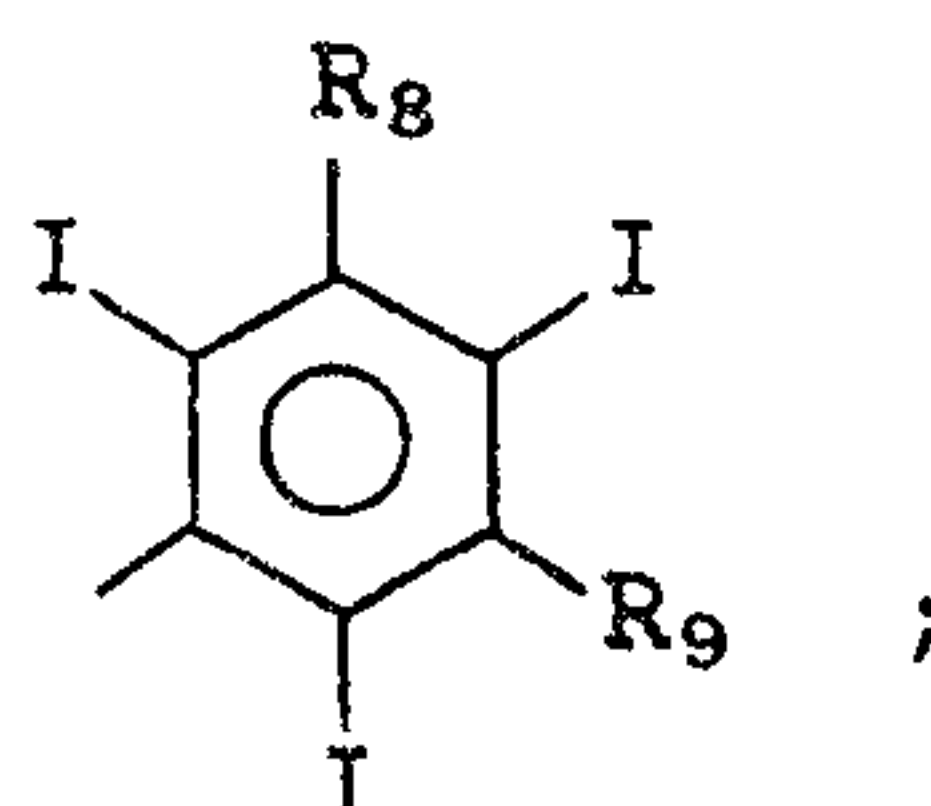
25 R_2 is $\begin{array}{c} \text{O} \text{ } R_5 \\ \parallel \quad | \\ -\text{C}-\text{N}-R_7 \end{array}$;

R_3 is heterocyclo;

or

R_2 can be $-\text{W}-\text{Z}$, where Z is

30



RA58

-8-

W is a linking group;
and wherein

5 R_8 is $\begin{array}{c} \text{O} \quad R_{10} \\ \parallel \quad | \\ -\text{C}-\text{N}-R_{12} \end{array}$ or heterocyclo;

R_9 is $\begin{array}{c} \text{O} \quad R_{11} \\ \parallel \quad | \\ -\text{C}-\text{N}-R_{13} \end{array}$ or heterocyclo;

R_4 , R_5 , R_{10} and R_{11} are the same or different and are hydrogen, methyl or $-\text{CH}_2\text{CH}_2\text{OH}$;

10 R_6 , R_7 , R_{12} and R_{13} are the same or

different and are hydrogen, $\text{HOCH}_2-\text{C}(\text{H})(\text{OH})-\text{CH}_2-$, $\text{CH}(\text{CH}_2\text{OH})_2$,

15 $-\text{CH}_2\text{CH}_2\text{OH}$, $\begin{array}{c} \text{CH}_2\text{OH} \\ | \\ -\text{CH} \\ | \\ \text{H}-\text{C}-\text{OH} \\ | \\ \text{H}-\text{C}-\text{OH} \\ | \\ \text{H} \end{array}$ and $\begin{array}{c} \text{CH}_2\text{OH} \\ | \\ -\text{CH} \\ | \\ \text{HO}-\text{C}-\text{H} \\ | \\ \text{CH}_2\text{OH} \end{array}$;

W is $-\text{X}-\text{Y}-\text{X}-$ wherein

20 X is $\begin{array}{c} -\text{N}-\text{CO}- \\ | \quad \quad | \\ R_{14} \quad \quad R_{14} \end{array}$ or $\begin{array}{c} -\text{CO}-\text{N}- \\ | \quad \quad | \\ R_{14} \quad \quad R_{14} \end{array}$;

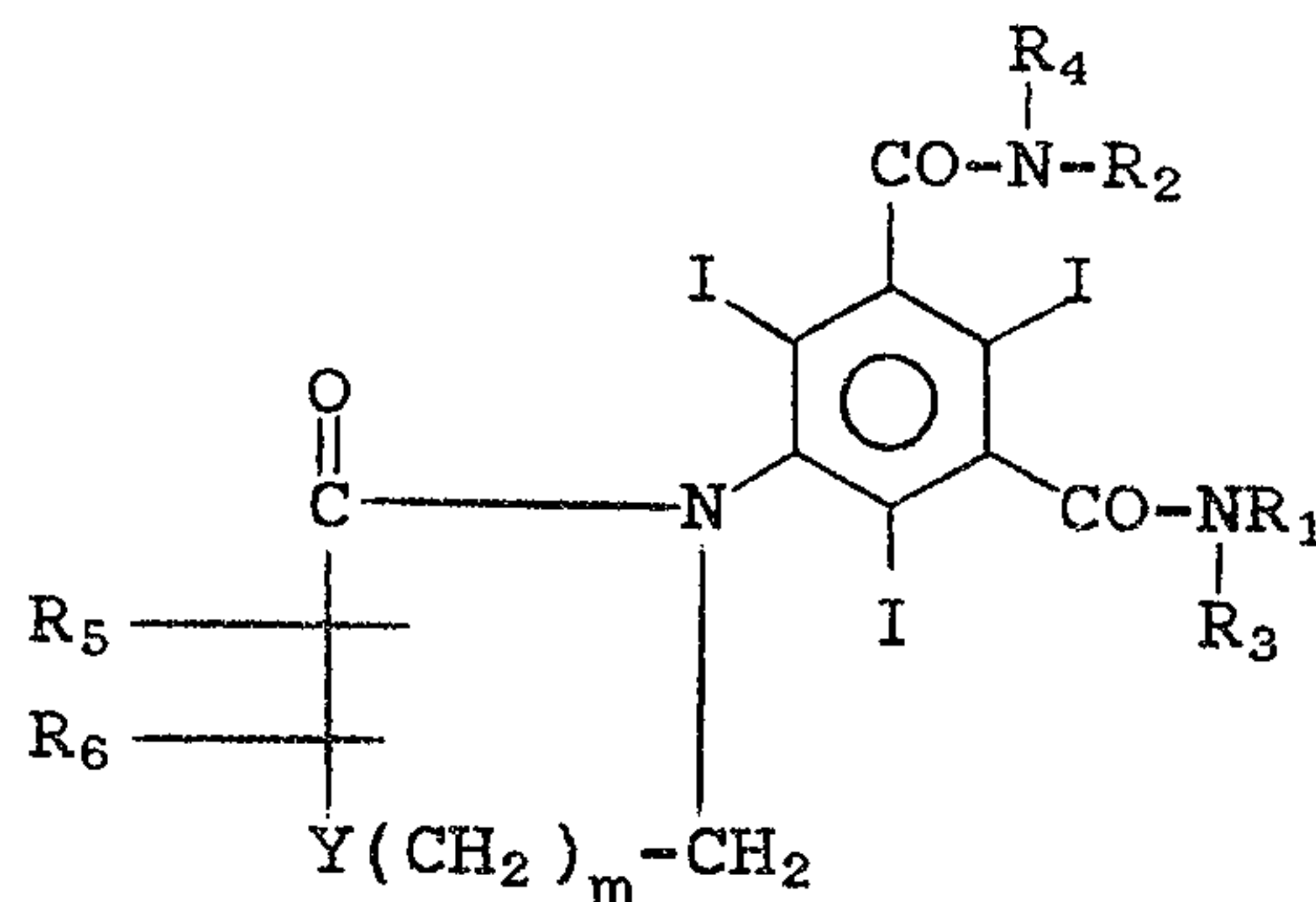
Y is $\begin{array}{c} -\text{CH}-\text{A}-(\text{CH})_n- \\ | \quad \quad | \\ R_{14} \quad \quad R_{14}' \end{array}$

25 R_{14} and R_{14}' are independently H, alkyl or hydroxyalkyl;

A is a single bond, $-\text{O}-$, $-\text{S}-$ or $-\text{N}-\text{COR}_{14}$;
n is 0 to 6.

30 Examples of triiodinated phenyl compounds having heterocyclic groups from category (A) have been disclosed, such as compounds of the formula

5

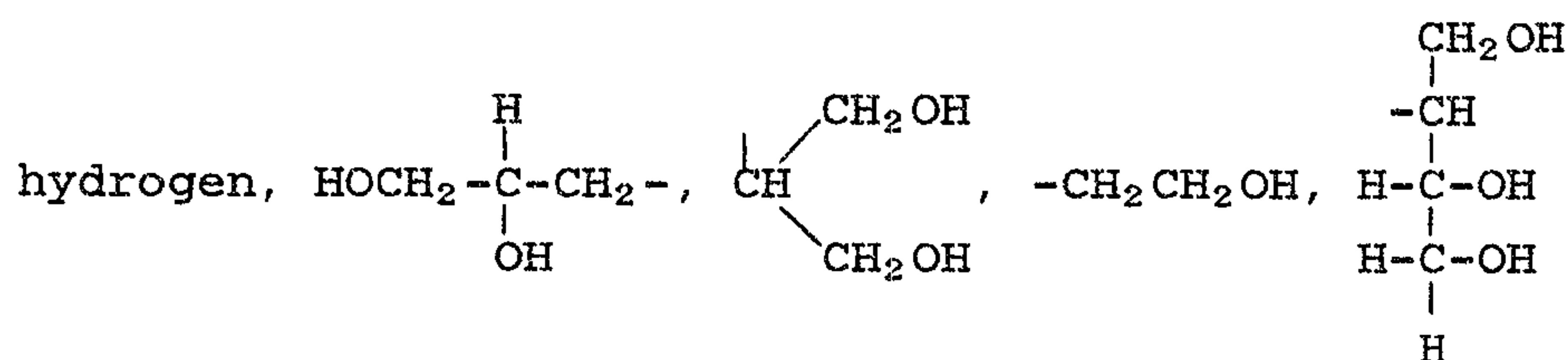


10 wherein Y is a single bond, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{O}-$,
 $-\text{OCH}_2-$, $-\text{N}-\text{CH}_2-$, $-\text{CH}_2-\text{N}-\text{C}-$, $-\text{CH}_2\text{N}-$, $-\text{CH}_2-$, $-\text{O}-$,
 O

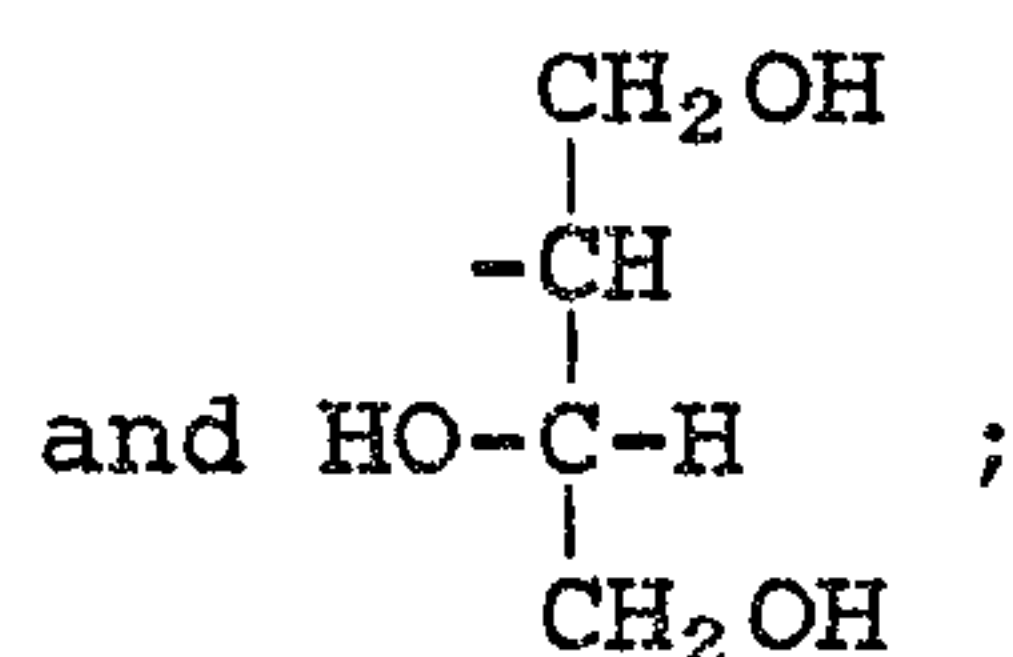
$-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ and $-\text{N}-$;

R_1 and R_2 are the same or different and are

15



20



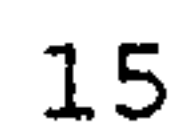
R_3 and R_4 are the same or different and are
 25 hydrogen, methyl or $-\text{CH}_2\text{CH}_2\text{OH}$;

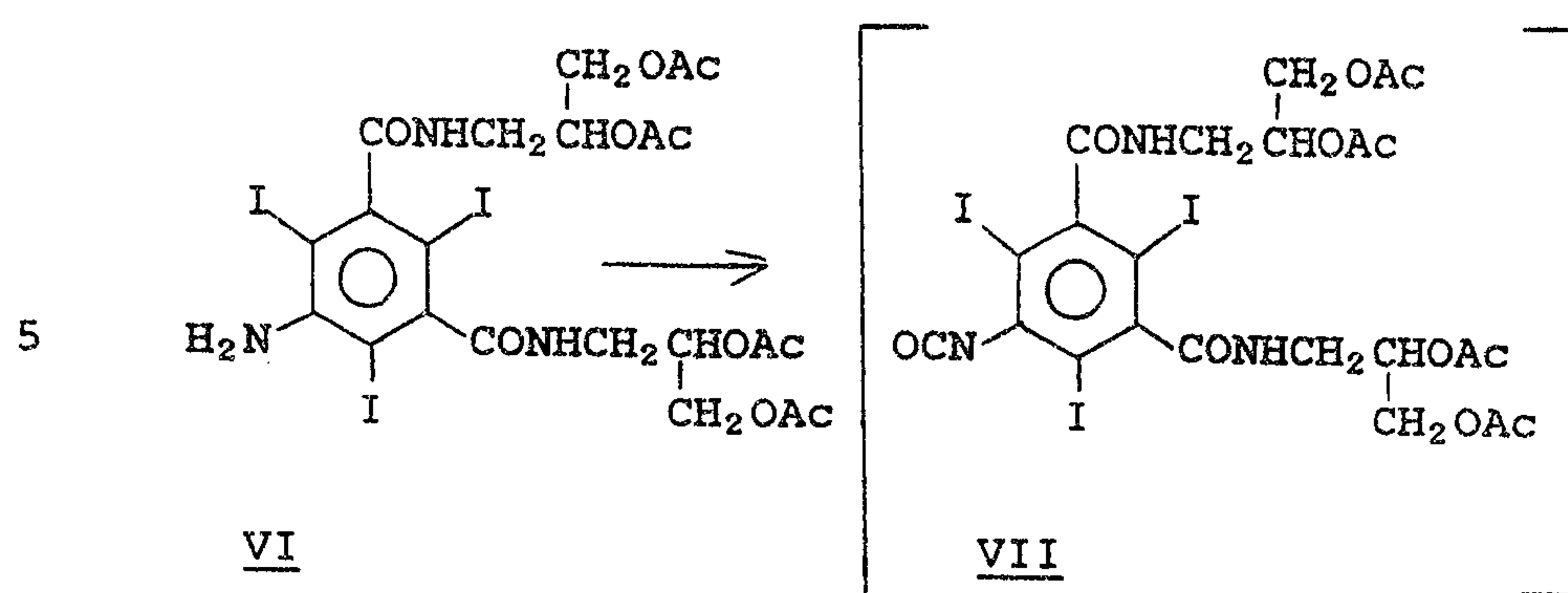
R_5 is hydrogen, alkyl, $-\text{CH}_2\text{CH}_2\text{OH}$, CH_2OH or
 OH; and

R_6 is alkyl, $-\text{CH}_2\text{CH}_2\text{OH}$, CH_2OH , OH or
 hydrogen and may be the same or different than R_5

30 and m is zero or one, with the proviso that no
 methylene or methine carbon atom of the
 heterocyclic ring is attached to both a nitrogen
 and an oxygen atom with the additional proviso

10





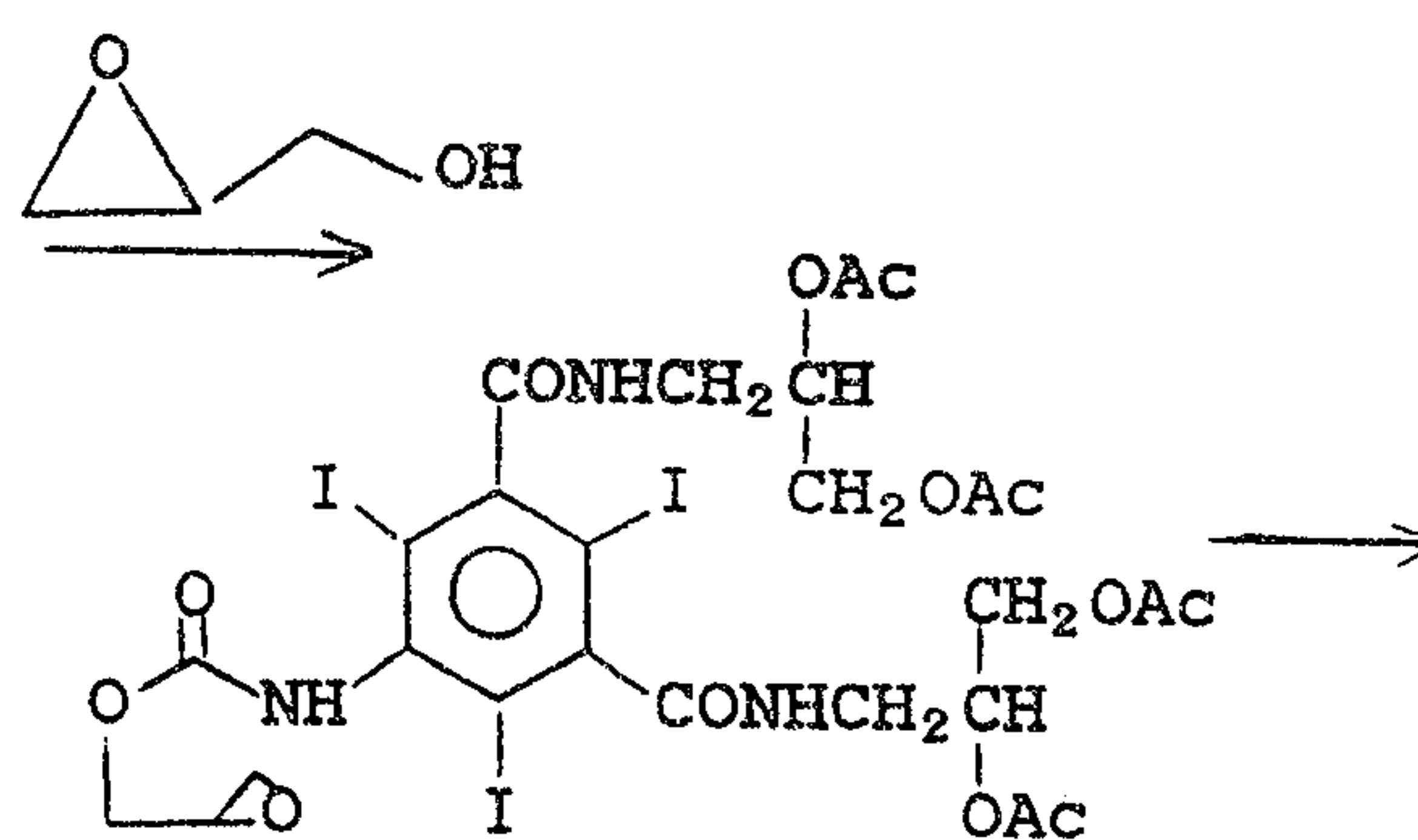
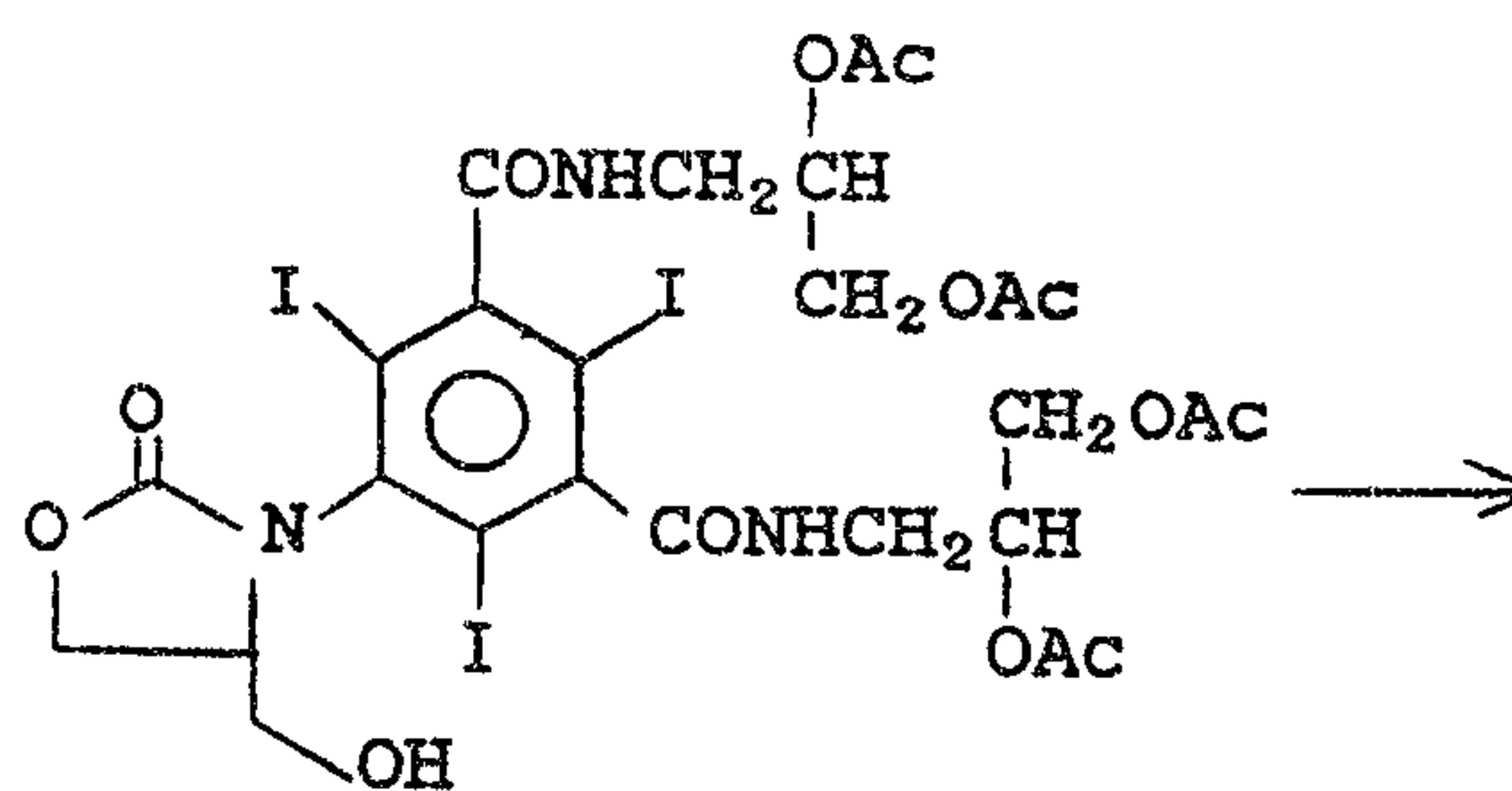
10

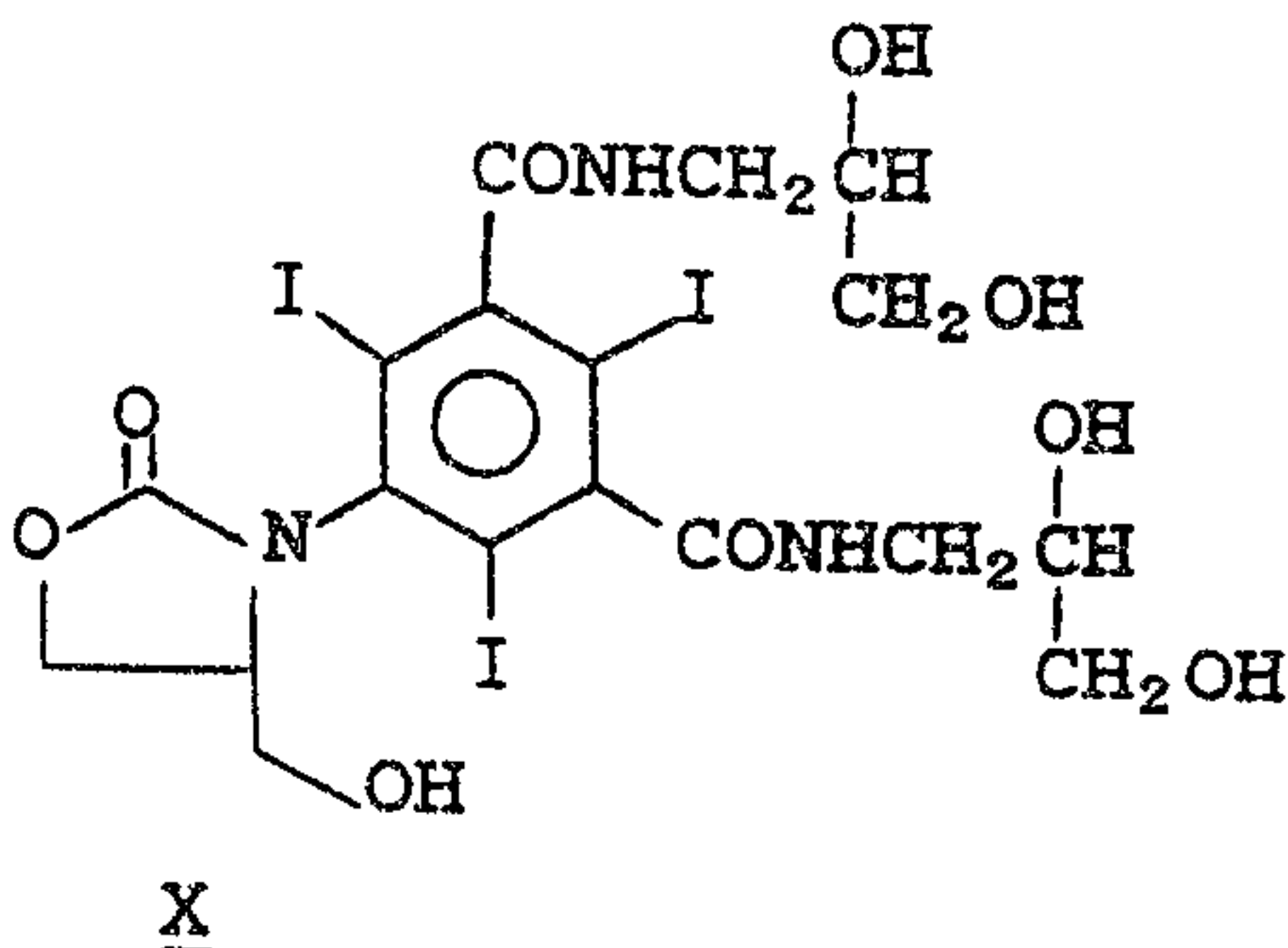
15

20

25

30

VIIIIX



10

Compound IA which is commercially available is iodinated with a compound such as potassium iododichloride in dilute hydrochloric acid solution to obtain 5-amino-2,4,6-triiodo-1,3-benzenedicarboxylic acid (II). Compound II is chlorinated with purified thionyl chloride to obtain the corresponding bis-chloride (III). Compound III is then amidated with 1-amino-2,3-propanediol (IV) to obtain the isophthalamide V. Compound V is then selectively O-acylated with acetic anhydride in pyridine to yield 5-amino-N,N'-bis [2,3-bis(acetyloxy)propyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (VI). Aminodehalogenation of compound VI by treatment with a toluene solution of phosgene in ethyl acetate at 60° over a period of sixteen hours results in a conversion into the corresponding isocyanate (VII). When the reaction is over, the solvents along with unreacted excess phosgene and hydrogen chloride, that was liberated during the course of the reaction, are removed by

15

20

25

30

distillation. Any trace of acid left behind, is removed by repeated co-distillations with ethyl acetate.

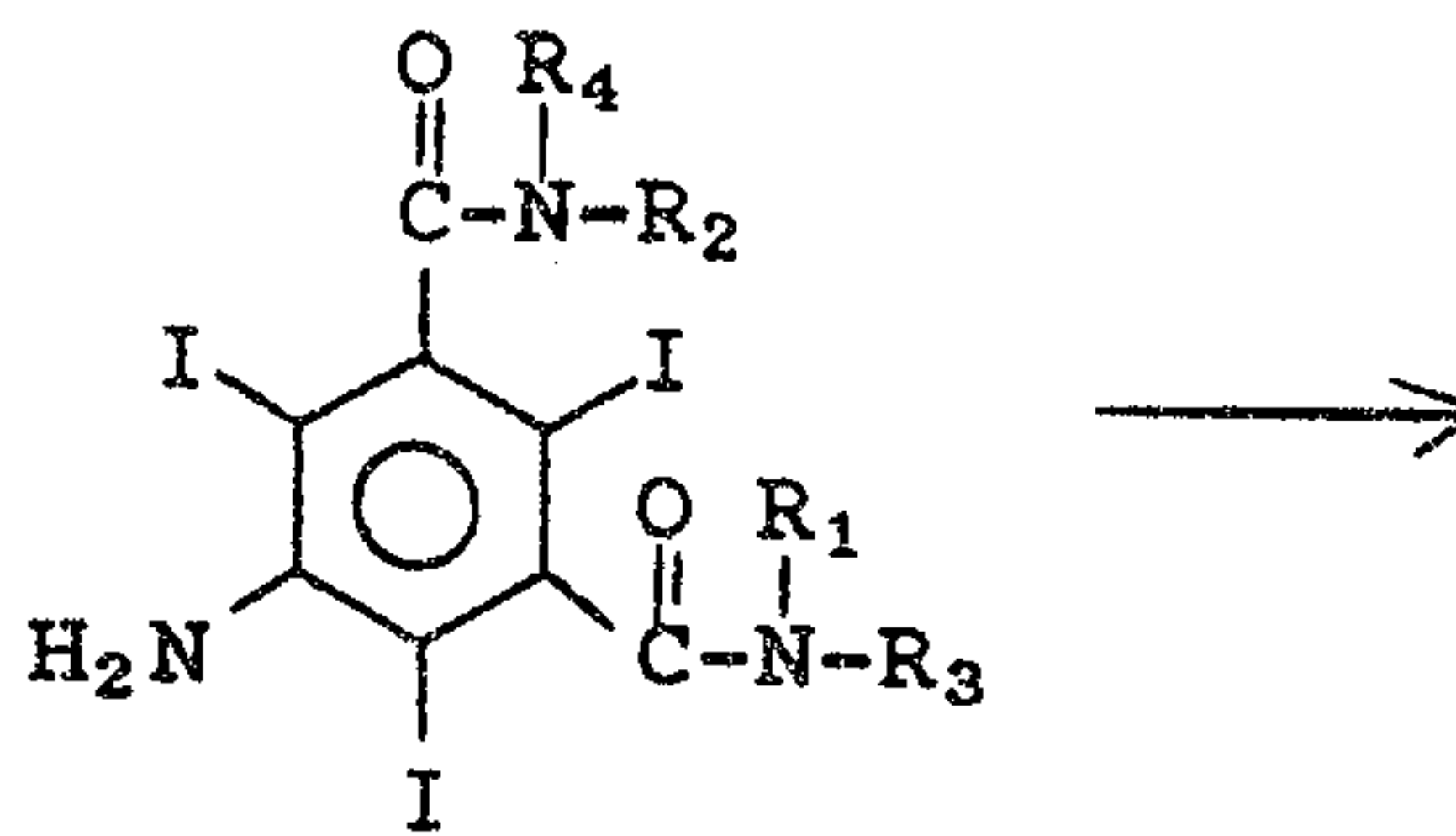
5 Addition of glycidol to the crude
isocyanate (VII), in the presence of catalysts
such as cuprous chloride or phenylmercuric
acetate, in ethyl acetate at room temperature
overnight yields oxiranylmethyl [3,5-bis[[[2,3-
10 bis(acetyloxy)propyl]amino]carbonyl-2,4,6-tri-
iodophenyl]carbamate (VIII).

A basic solution of the glycidyl carbamate
(VIII) is heated at 75° for 30 minutes.
Intramolecular cyclization occurs to afford N,N'-
bis[2,3-bis(acetyloxy)propyl]-5-[4-hydroxymethyl)-
15 2-oxo-3-oxazolidinyl]-2,4,6-triiodo-1,3-benzene-
dicarboxamide (IX), as the sole product, after
crystallization from aqueous methanol.

Deacetylation of the tetraacetate (IX) by
treatment with sodium methoxide in methanol,
20 followed by neutralization with Dowex-50(H⁺) resin
and decolorization with charcoal, yields N,N'-bis-
(2,3-dihydroxypropyl)-5-[4-(hydroxymethyl)-2-oxo-
3-oxazolidinyl]-2,4,6-triiodo-1,3-benzenedicarbox-
amide (X). This product is desalted and further
25 purified by low pressure reverse phase column
chromatography. Crystallization from water or
from aqueous isopropanol yields compound X.

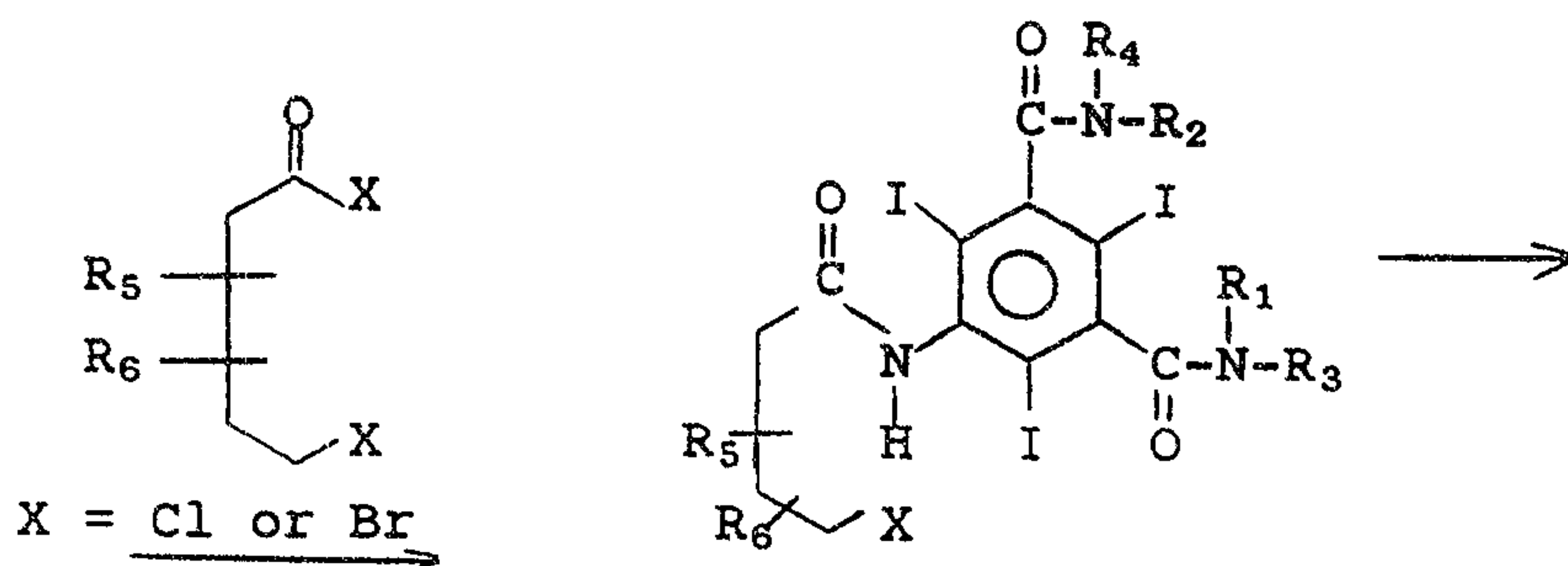
Substituted pyrrolidin-2-one derivatives
with no substitution at the 5 position are
30 prepared according to the following scheme:

5

XI

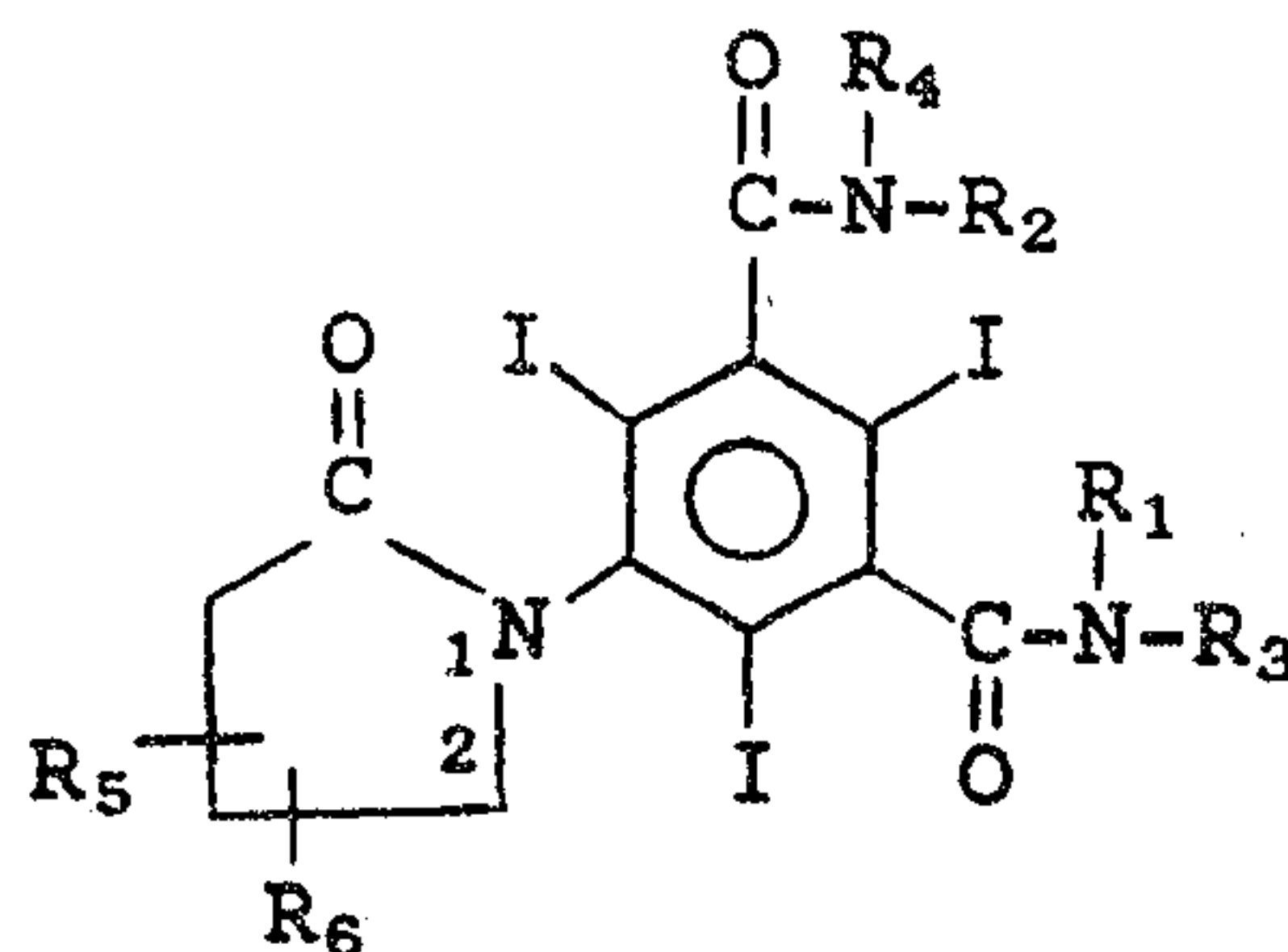
10

15

XII

20

25

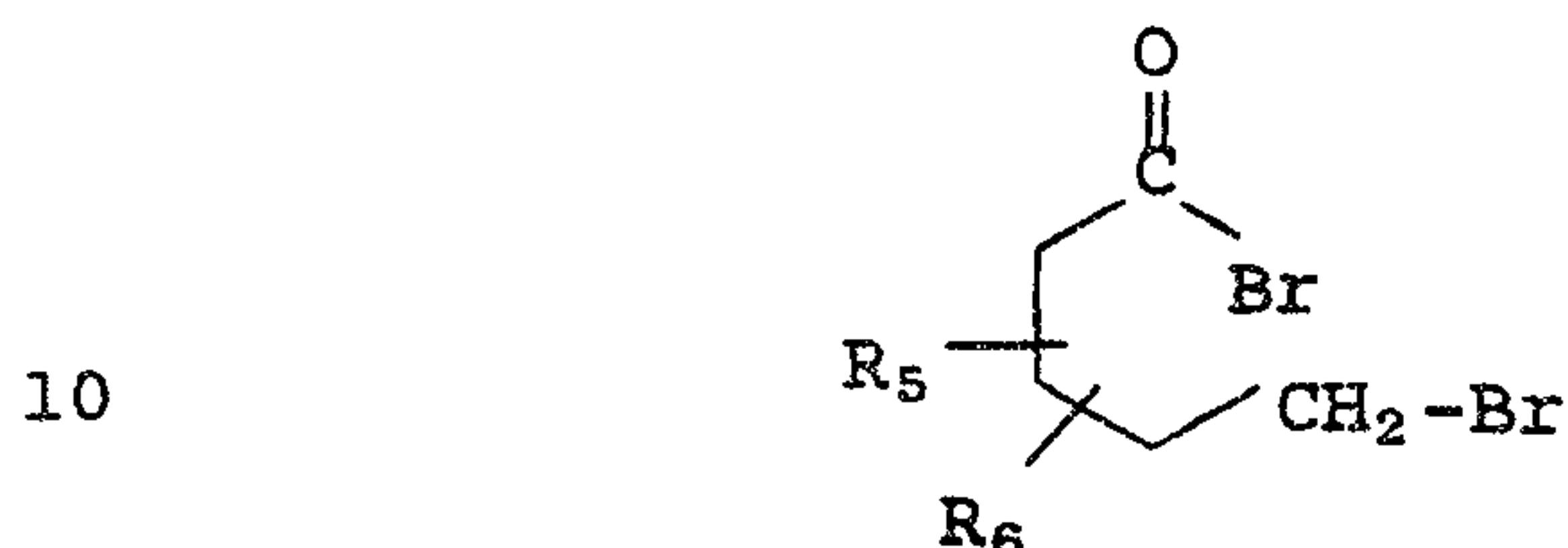
XIII

30

35

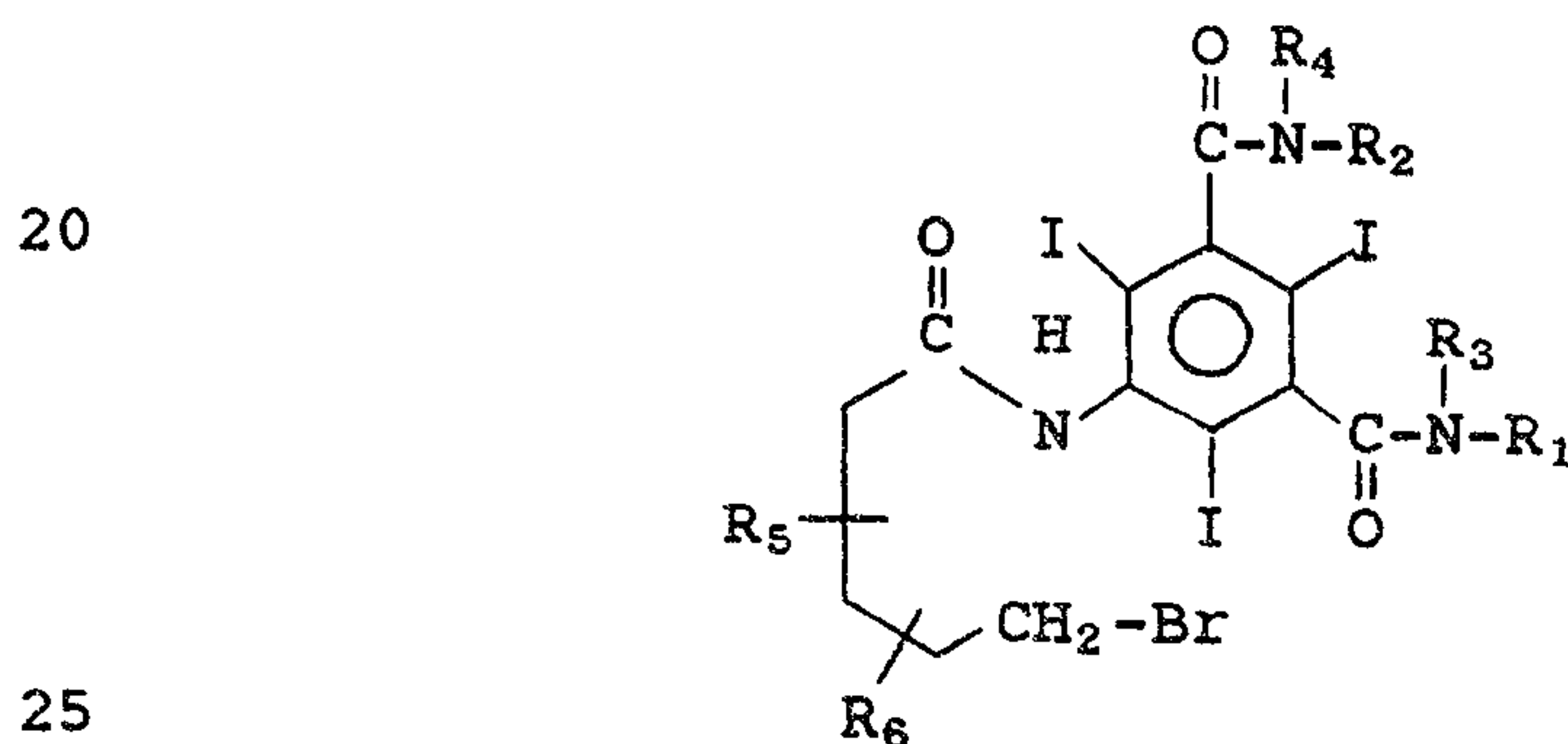
The amide of formula XI, which is formed using the methodology described in the previous scheme, is reacted with an ω -halo-acid halide to obtain the anilide of compound XII followed by cyclization of compound XII to the pyrrolidine-2-one of formula XIII.

The compounds of our copending application wherein the heterocyclic group is a piperidin-2-one can be prepared by reacting compound XI with an appropriately substituted bromopentanoyl bromide of the formula



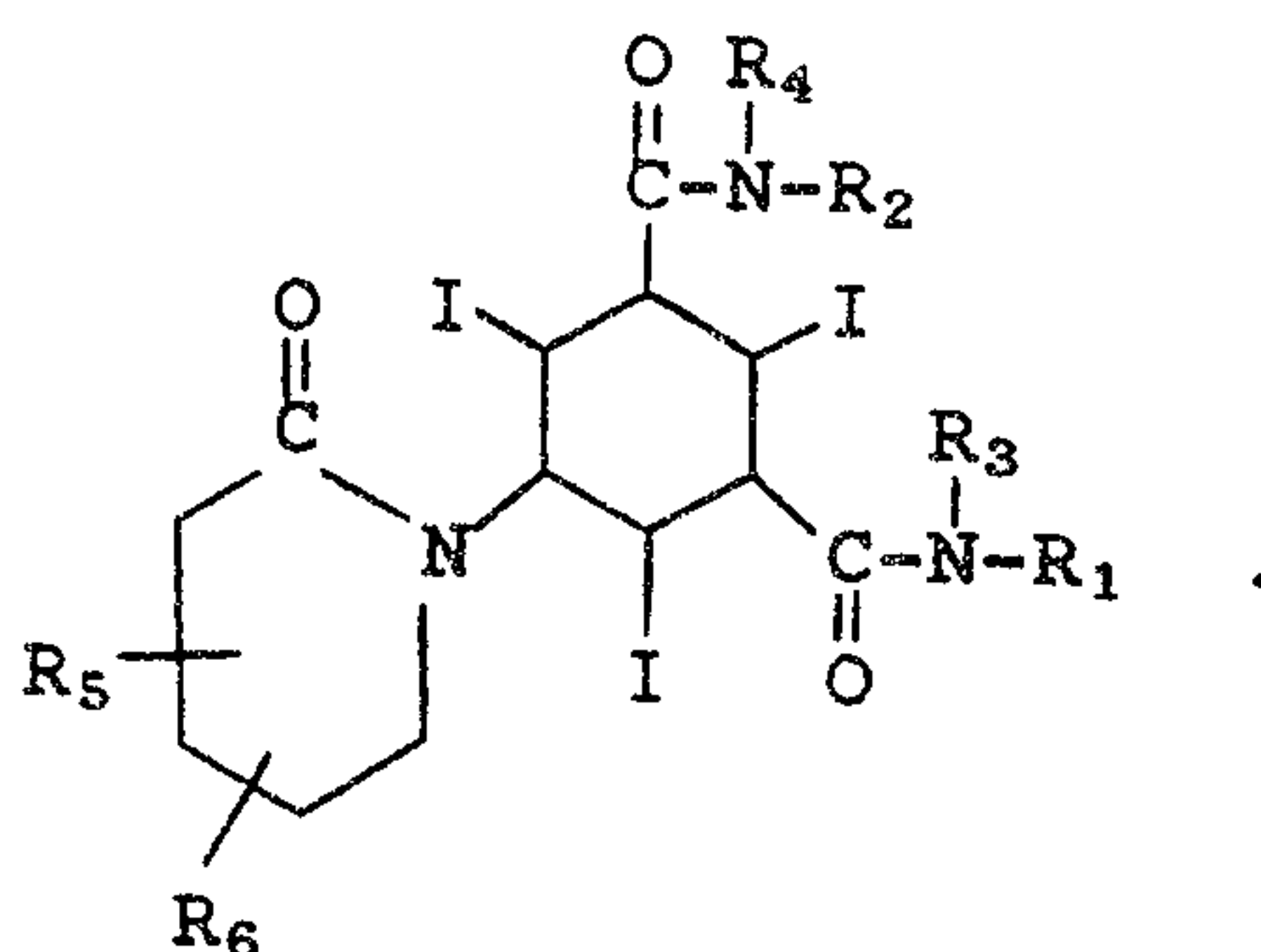
XIV

15 in a suitable solvent such as dimethylacetamide to yield the corresponding anilide of the formula

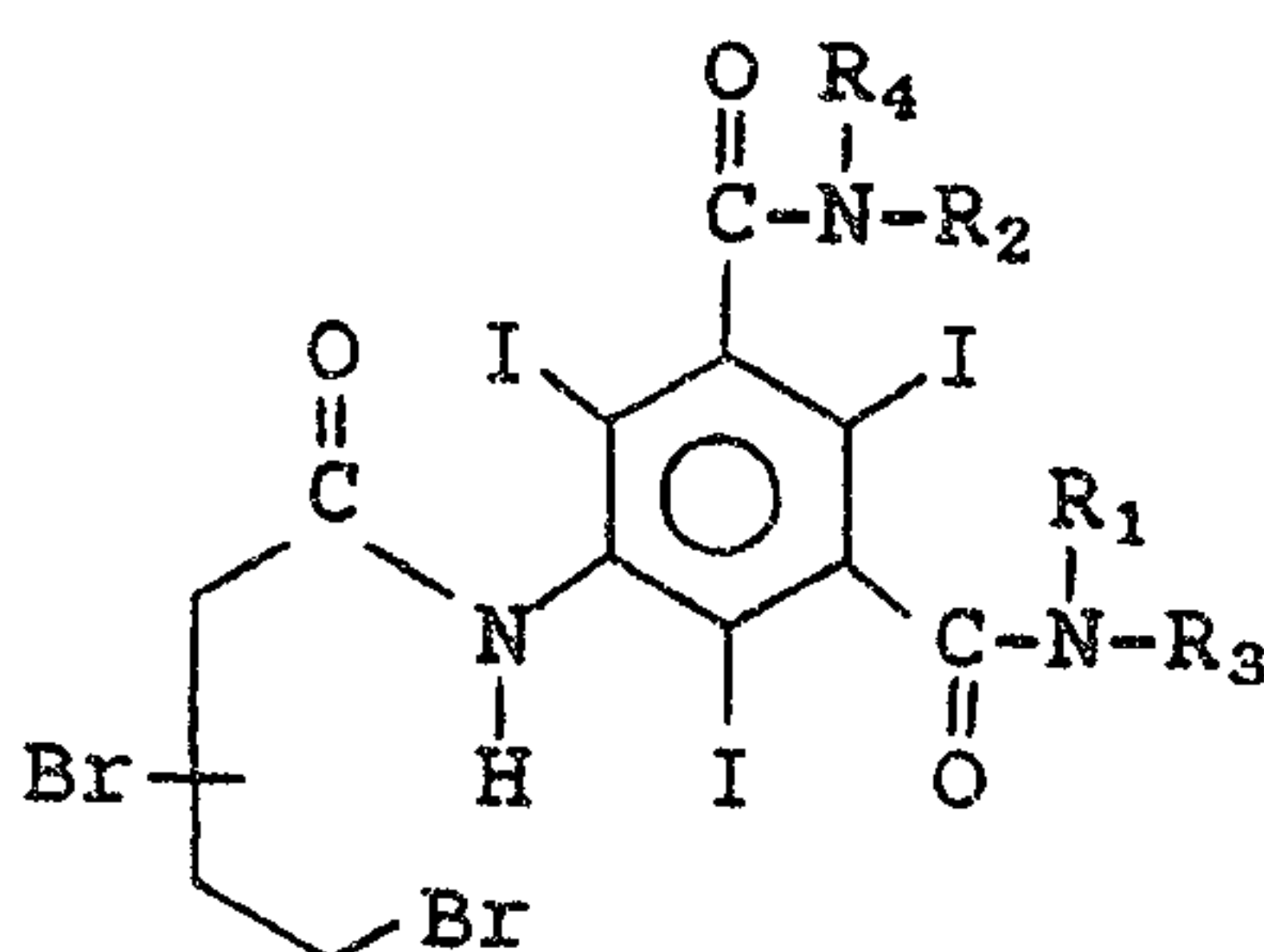


XV

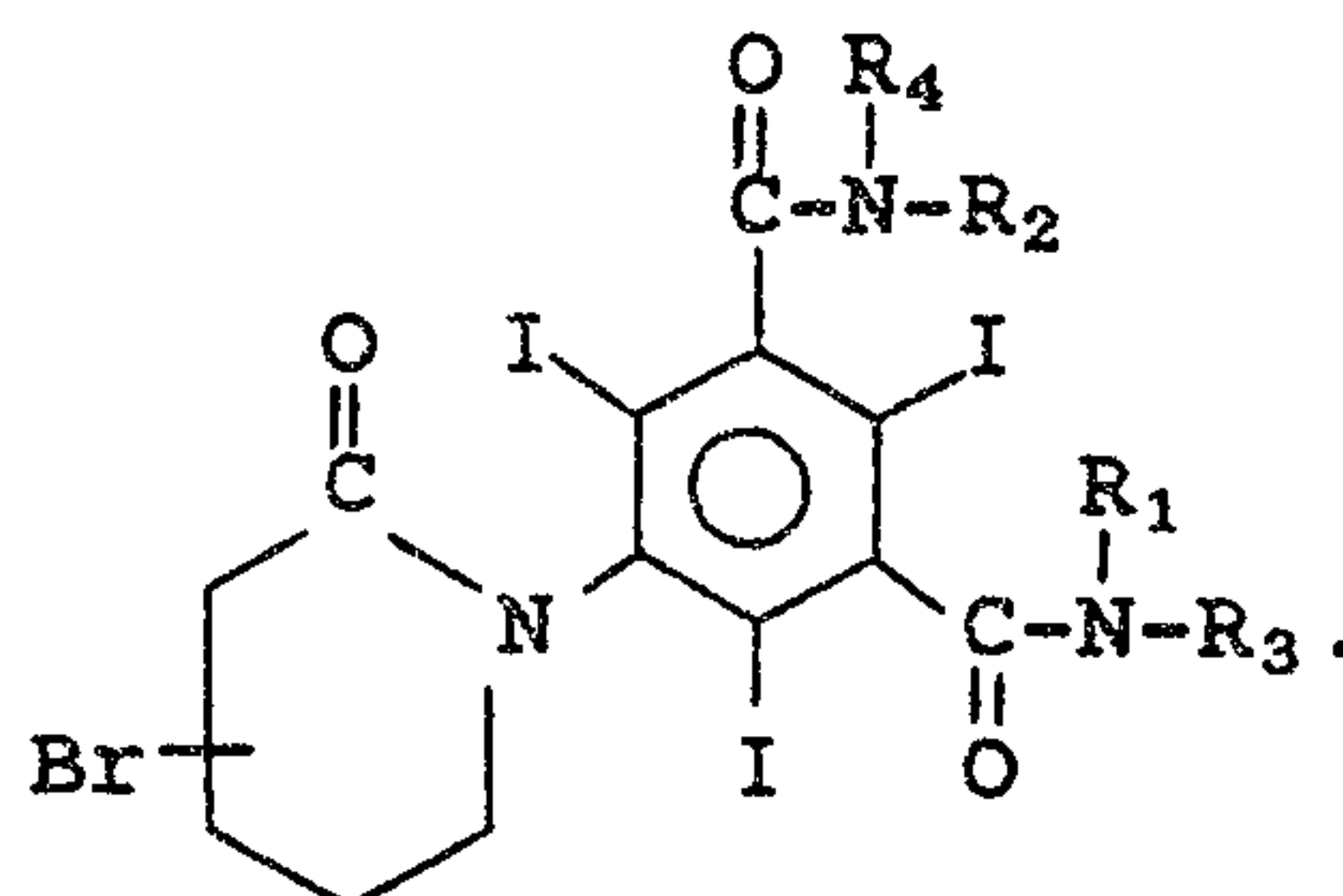
which upon treatment with a base such as potassium carbonate in a suitable solvent such as dimethylacetamide will yield the desired piperidin-2-one of the formula

XVI

When R_5 or R_6 is hydroxyl or hydroxymethyl in compound XVI it is protected as the corresponding acetate or ether which is eventually deprotected by conventional means. A halogen substituent on the piperidine-2-one ring can be converted into an acetyloxy group by treatment with silver acetate in acetic acid or with tetraethylammonium acetate in a suitable solvent. Solvolysis of the acetate with aqueous methanolic sodium hydroxide or methanol in the presence of sodium methoxide will give compound XVI wherein R_5 and/or R_6 is hydroxy or CH_2OH . For example, the dibromo-anilide

XVII

can be ring closed to the 3-bromo-piperidin-2-one

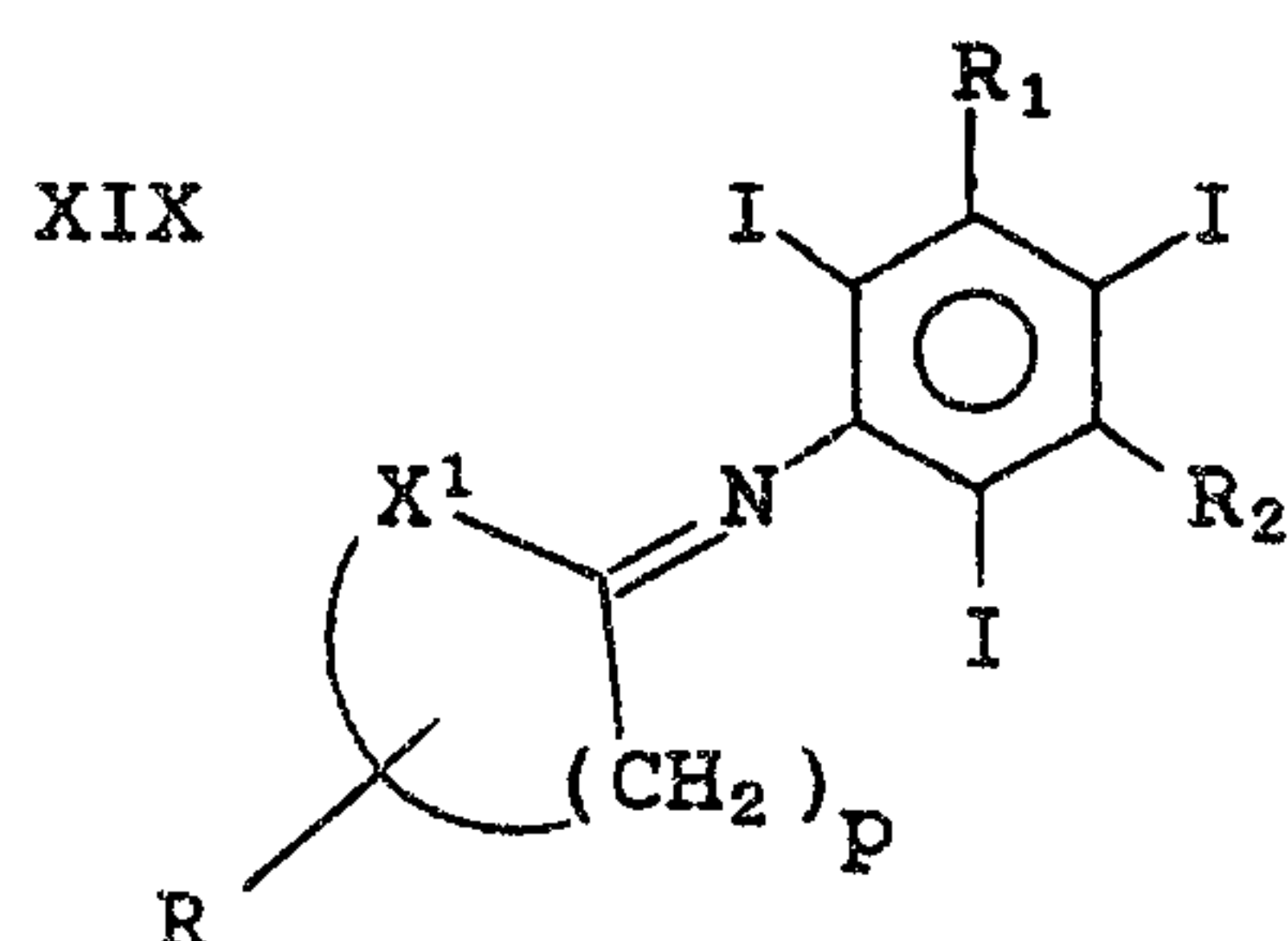


XVIII

The bromo moiety of compound XVIII can be converted into the acetate and then to the corresponding hydroxy compound by the methods described above.

2,5-Dibromopentanoyl bromide used in the preparation of compound XVII is prepared by treating δ -valerolactone with bromine in the presence of red phosphorous. 2,5-Dibromopentanoyl bromide is condensed with compound XI to form compound XVII.

Triiodinated phenyl derivatives of formula I having heterocyclic group (B) attached thereto are novel compounds shown by the formula



wherein R is selected from hydrogen, alkyl, hydroxy, alkoxy, hydroxyalkyl and alkoxyalkyl;

X^1 is $\begin{array}{c} \text{O} \\ \parallel \\ \text{N}-\text{CH} \\ | \end{array}$, $\begin{array}{c} \text{O} \\ \parallel \\ \text{N}-\text{Calkyl} \\ | \end{array}$, -S- or -O-;

5

p is 2-5;

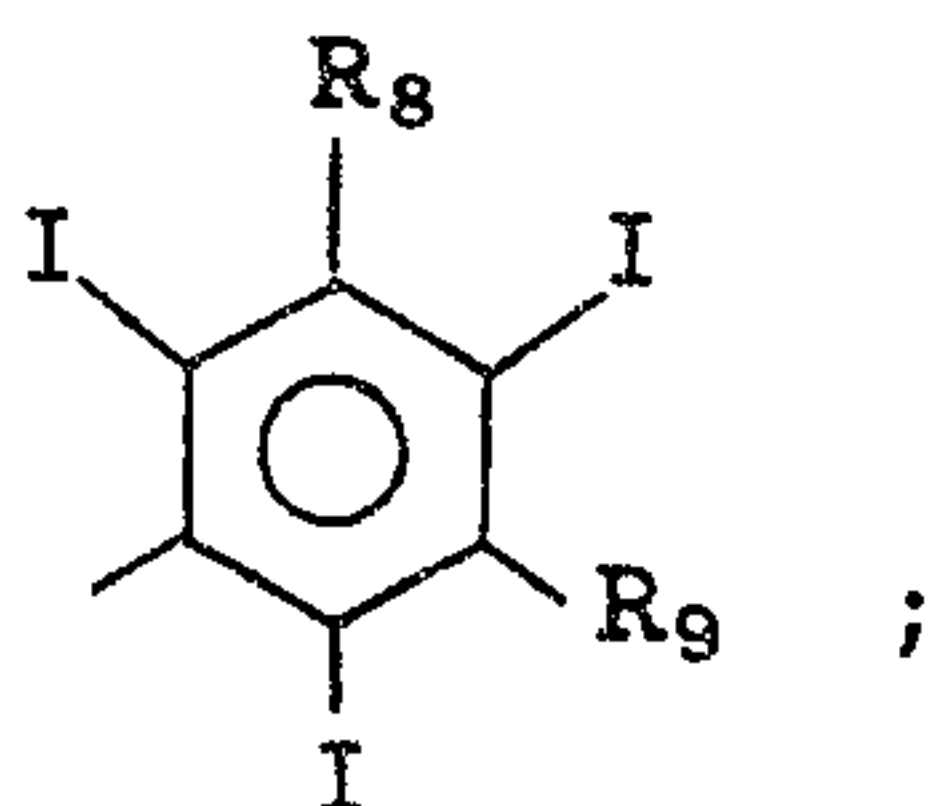
R_1 is $\begin{array}{c} \text{O} \text{ } R_4 \\ \parallel \quad | \\ -\text{C}-\text{N}-R_6 \end{array}$;

10

R_2 is $\begin{array}{c} \text{O} \text{ } R_5 \\ \parallel \quad | \\ -\text{C}-\text{N}-R_7 \end{array}$; or

R_2 can also be -W-Z, where Z is

15



W is a linking group
and wherein

20

R_8 is $\begin{array}{c} \text{O} \text{ } R_{10} \\ \parallel \quad | \\ -\text{C}-\text{N}-R_{12} \end{array}$ or heterocyclo;

R_9 is $\begin{array}{c} \text{O} \text{ } R_{11} \\ \parallel \quad | \\ -\text{C}-\text{N}-R_{13} \end{array}$ or heterocyclo;

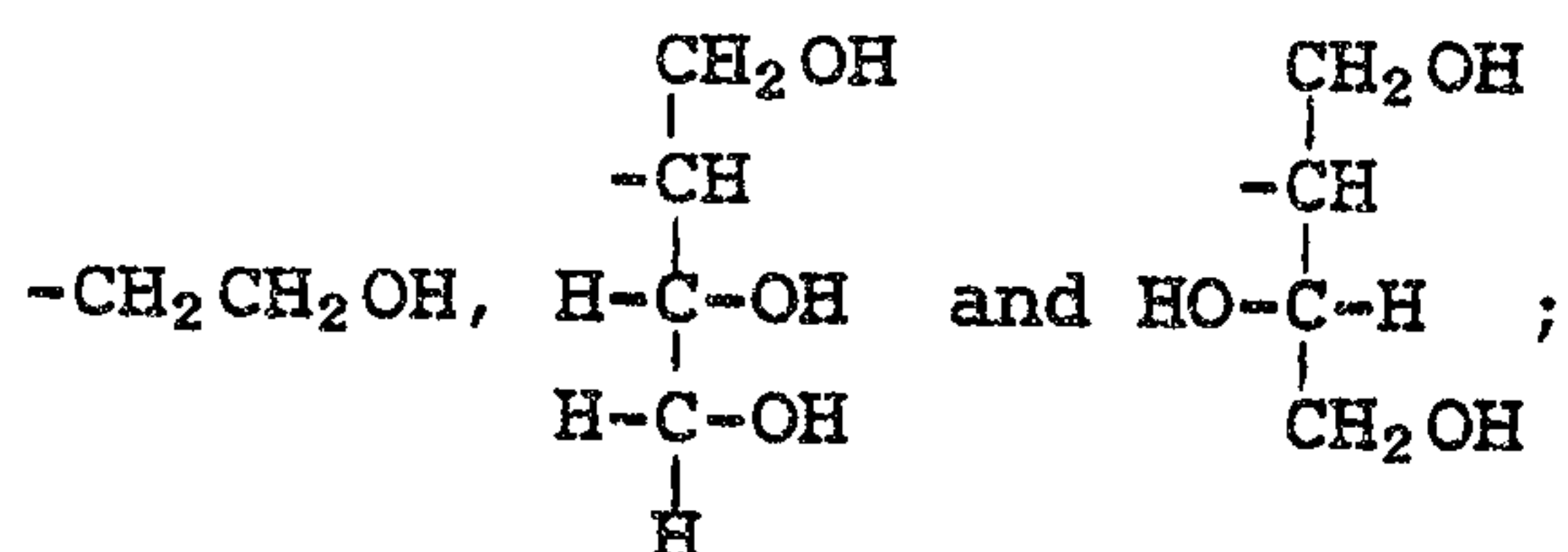
25

R_4 , R_5 , R_{10} and R_{11} are the same or different and are hydrogen, methyl or -CH₂CH₂OH;

R_6 , R_7 , R_{12} and R_{13} are the same or

30

different and are $\text{HOCH}_2-\begin{array}{c} \text{H} \\ | \\ \text{C}-\text{CH}_2- \\ | \\ \text{OH} \end{array}$, $\begin{array}{c} \text{CH}_2\text{OH} \\ | \\ \text{CH} \\ | \\ \text{CH}_2\text{OH} \end{array}$,



5

W is -X-Y-X- wherein

X is $\begin{array}{c} -\text{N}-\text{CO}- \\ | \\ \text{R}_{14} \end{array}$ or $\begin{array}{c} -\text{CO}-\text{N}- \\ | \\ \text{R}_{14} \end{array}$;

Y is $\begin{array}{c} -\text{CH}-\text{A}-(\text{CH})_n- \\ | \quad | \\ \text{R}_{14} \quad \text{R}_{14}' \end{array}$

10

R_{14} and R_{14}' is H, alkyl or hydroxyalkyl;
A is a single bond, -O-, -S- or -N-COR₁₄;
n is 0 to 6.

In the definitions above and throughout
this application, the term "alkyl" refers to
branched or straight chain carbon groups of 1-6
atoms.

Preferred novel compounds of formula XIX
are those wherein

20

X¹ is oxygen;

p is 3;

R is hydroxyalkyl;

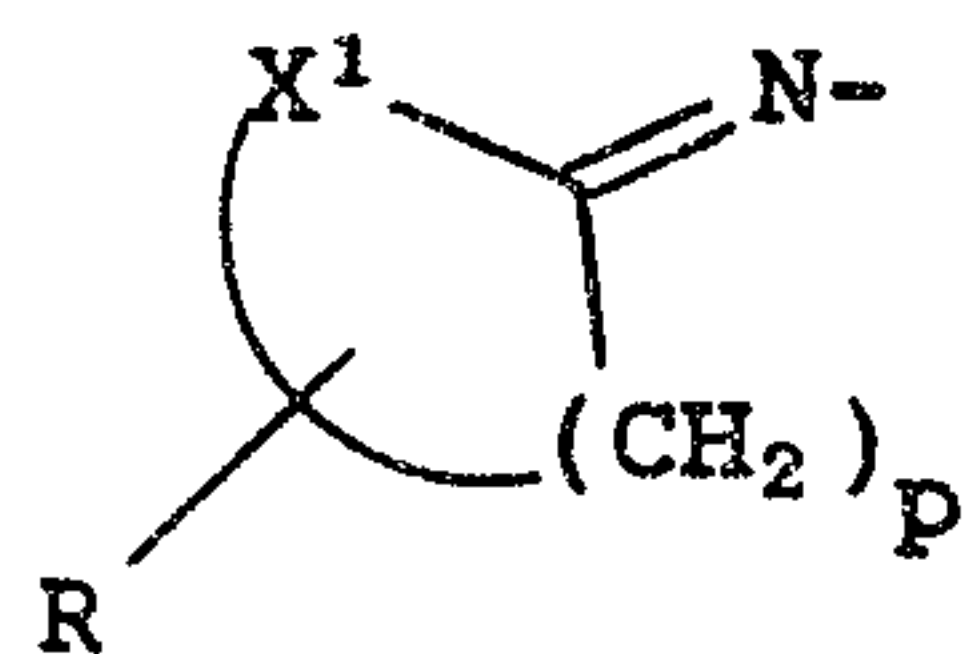
R₄ and R₅ are each hydrogen; and

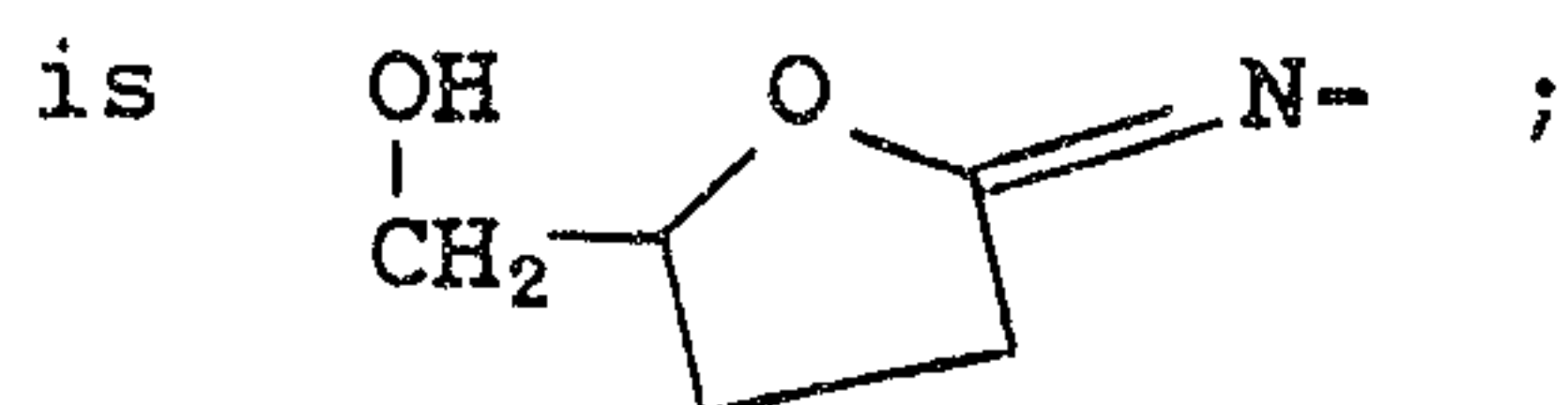
R₆ and R₇ are each hydroxyalkyl.

25

Most preferred of the novel compounds of
the present invention wherein

30





R_4 and R_5 are each hydrogen; and,

5

R_6 and R_7 are each $-\text{CH}_2\text{CH}(\text{OH})\text{CH}_2\text{OH}$ or $-\text{CH}_2\text{CH}(\text{CH}_2\text{OH})_2$.

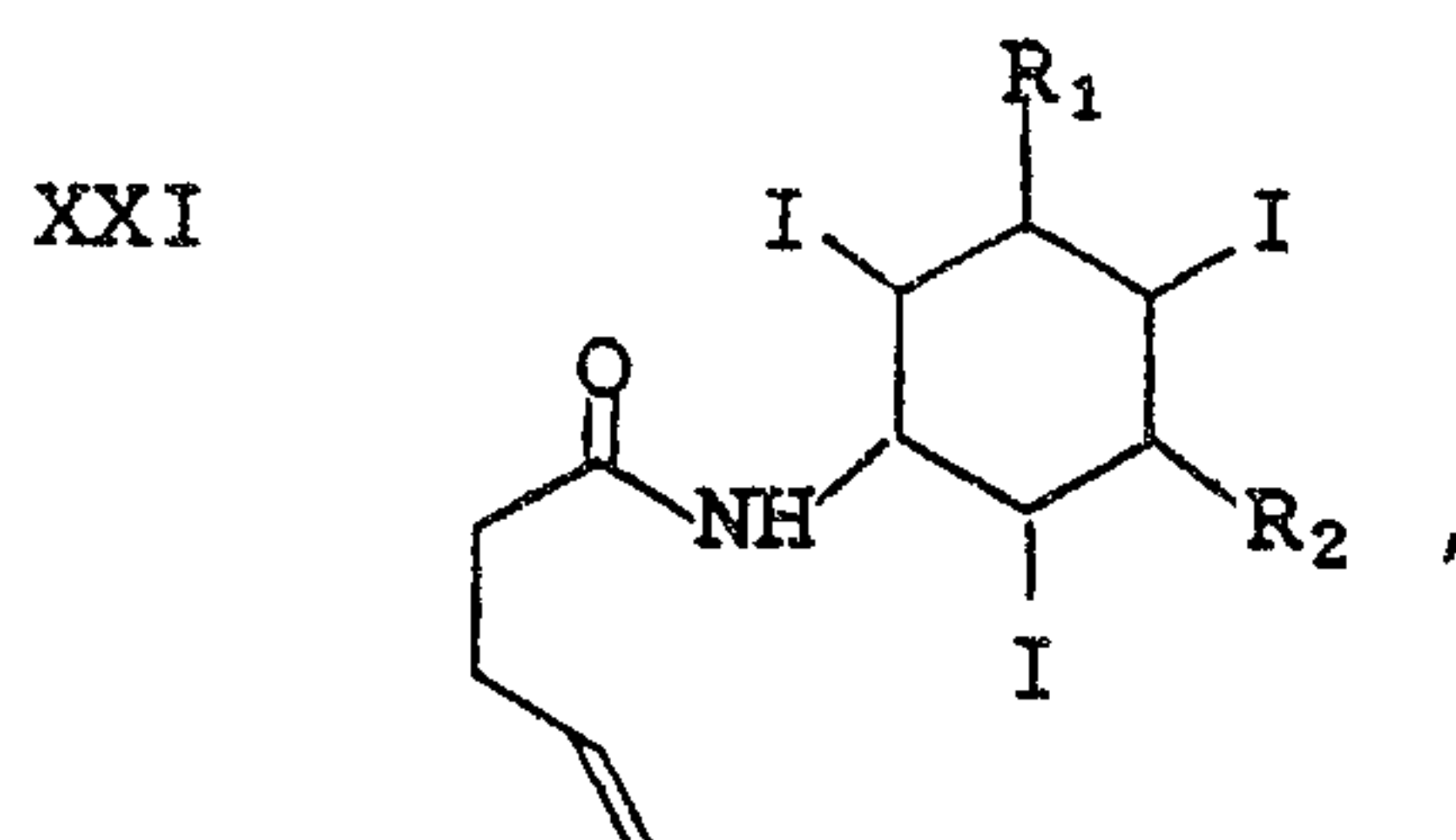
To prepare the novel compounds of the present invention, a compound of formula XI is treated with 4-pentenoyl chloride,

10



in an aprotic solvent, e.g., dimethylacetamide, to provide the corresponding pentenoyl anilide

15



20

where R_1 and R_2 are understood to be protected when they contain active functionalities, e.g., -OH, -SH and NHR groups. Final products in protected form can be deprotected using known methodology.

25

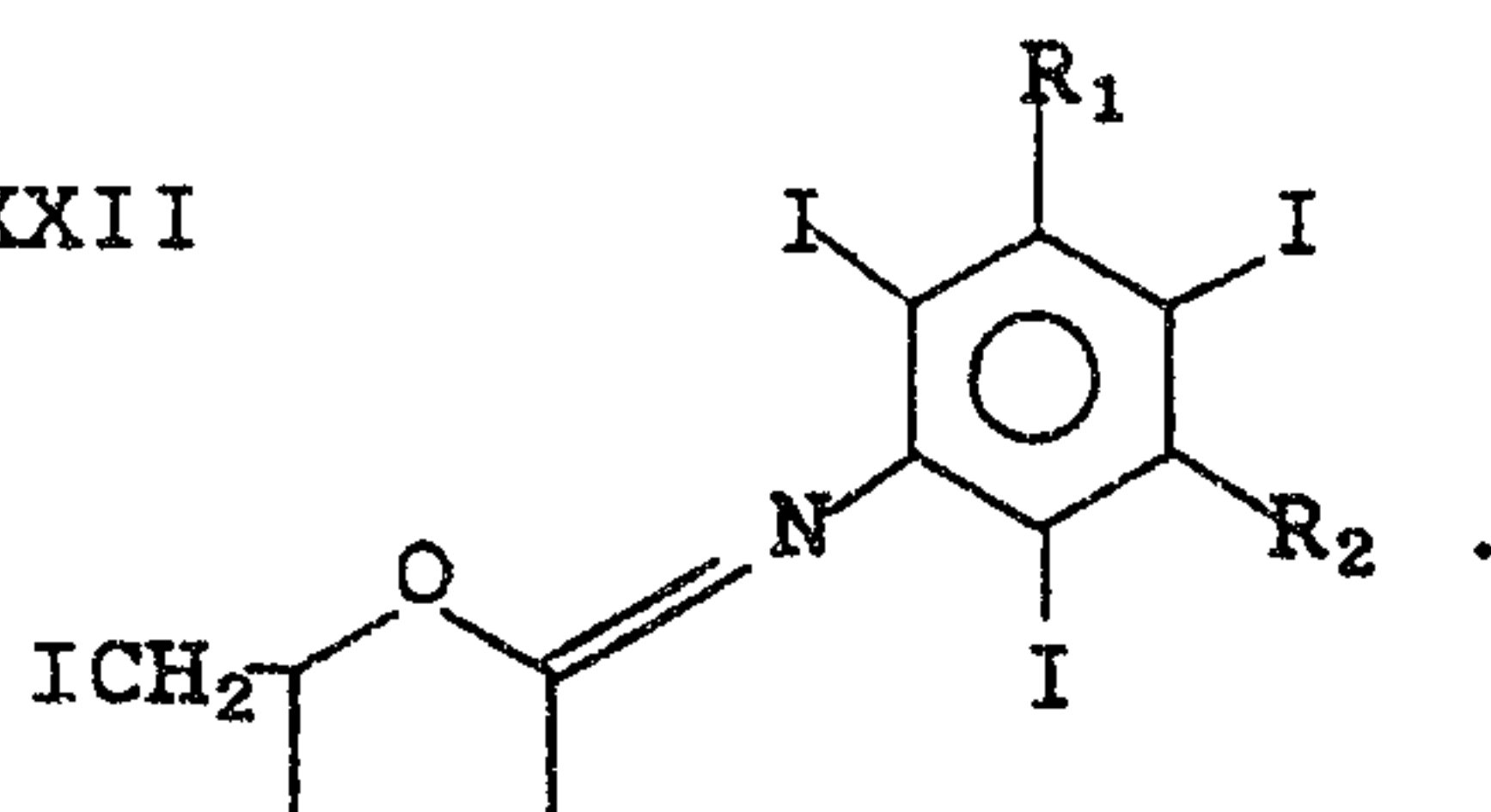
The 4-pentenoyl chloride XX was prepared from 4-pentenoic acid using known procedures. (Ascher, "Constitution of Isanic and Isanolic Acids, Ann.", 589, 222-38, 1954; Chem. Abs., 50, 1599.)

30

Compound XXI can thereafter be treated with N-iodosuccinimide in a solvent, e.g., chloroform, to provide

5

XXII

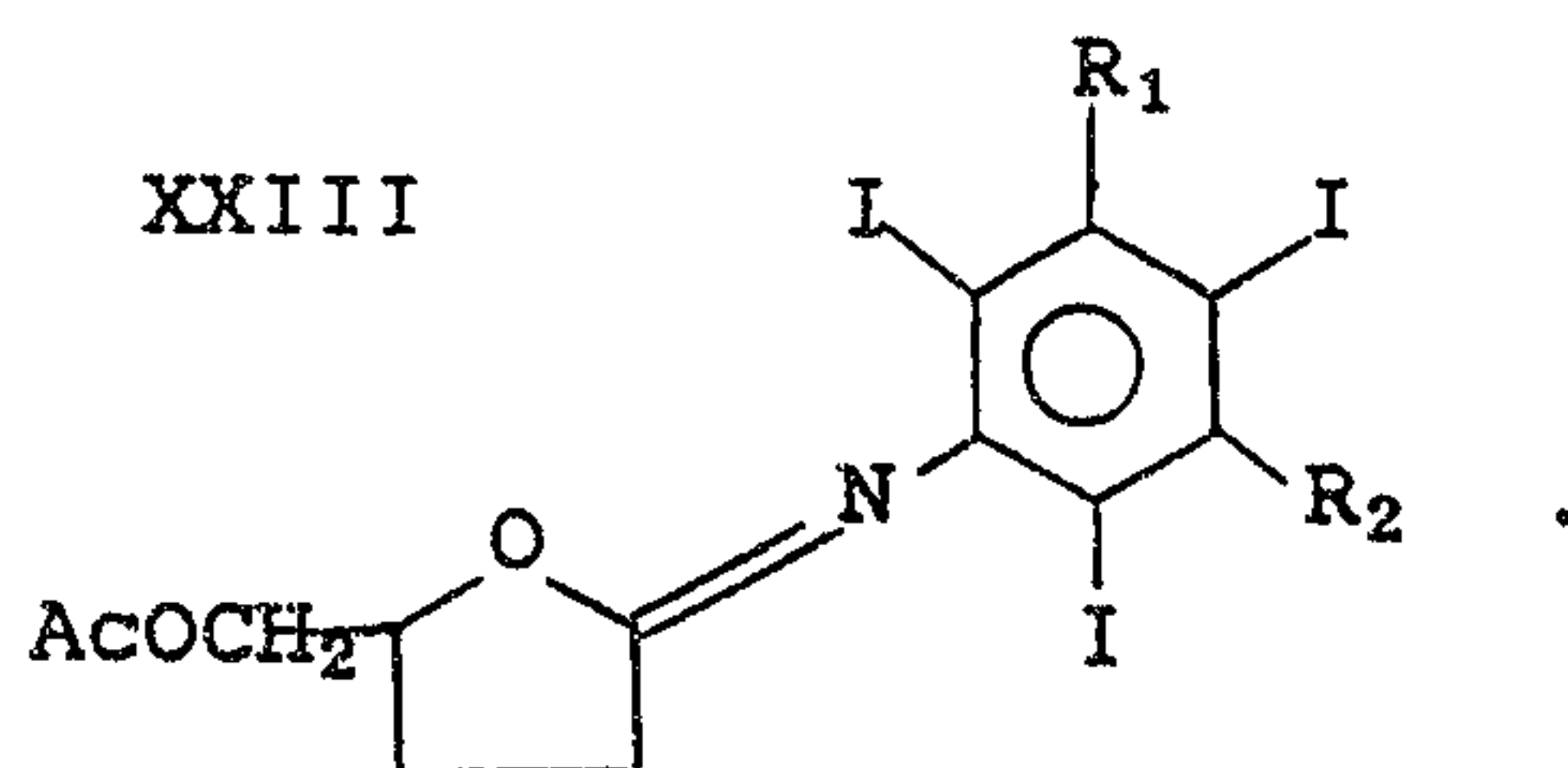


10

Compound XXII is then subjected to acetoxylation, e.g., by treatment with silver acetate in acetic acid to provide compounds of the formula

15

XXIII

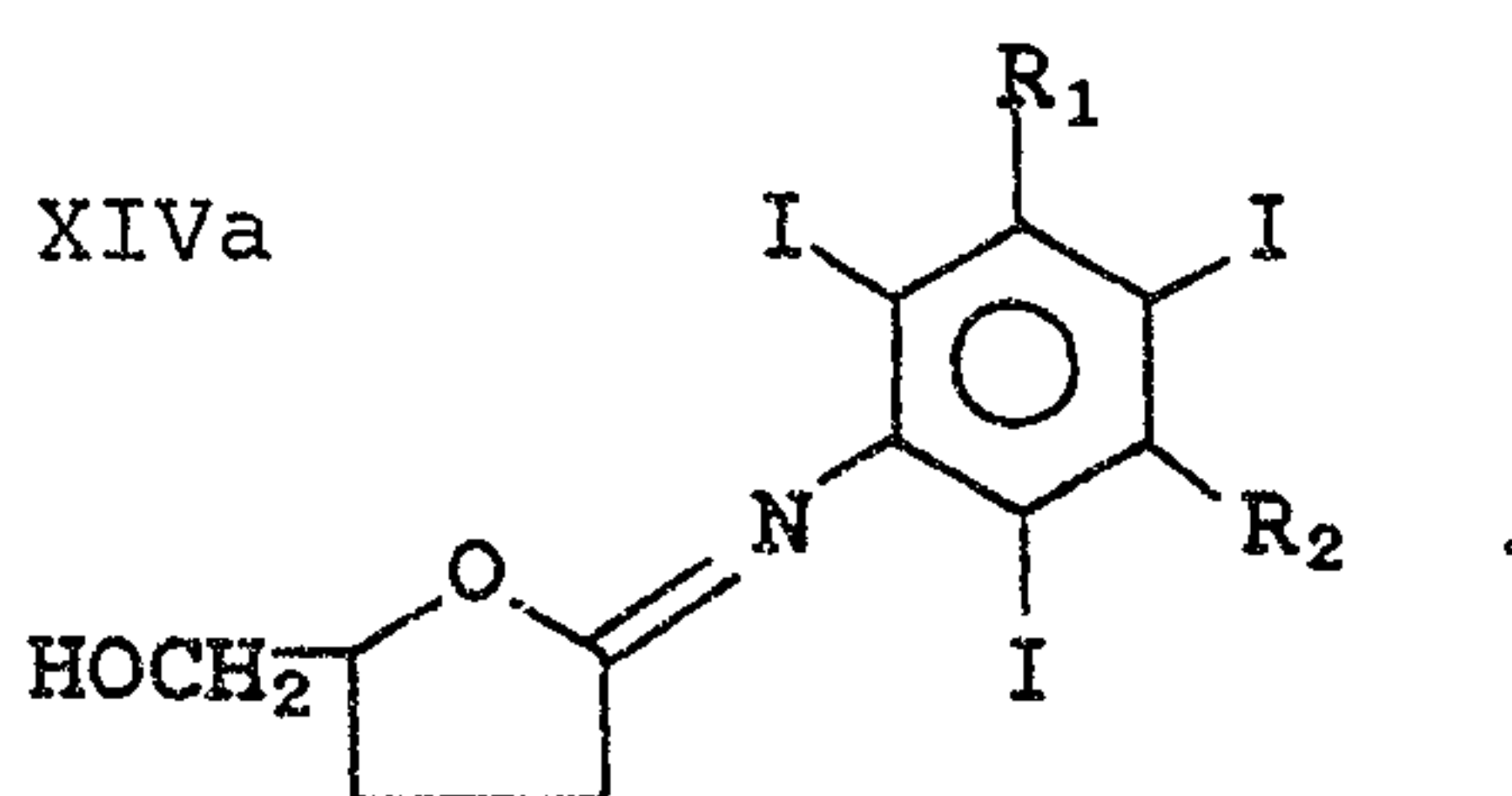


20

Deacetylation, such as by treatment with sodium methoxide in methanol, provides the desired product

25

XIVa



30

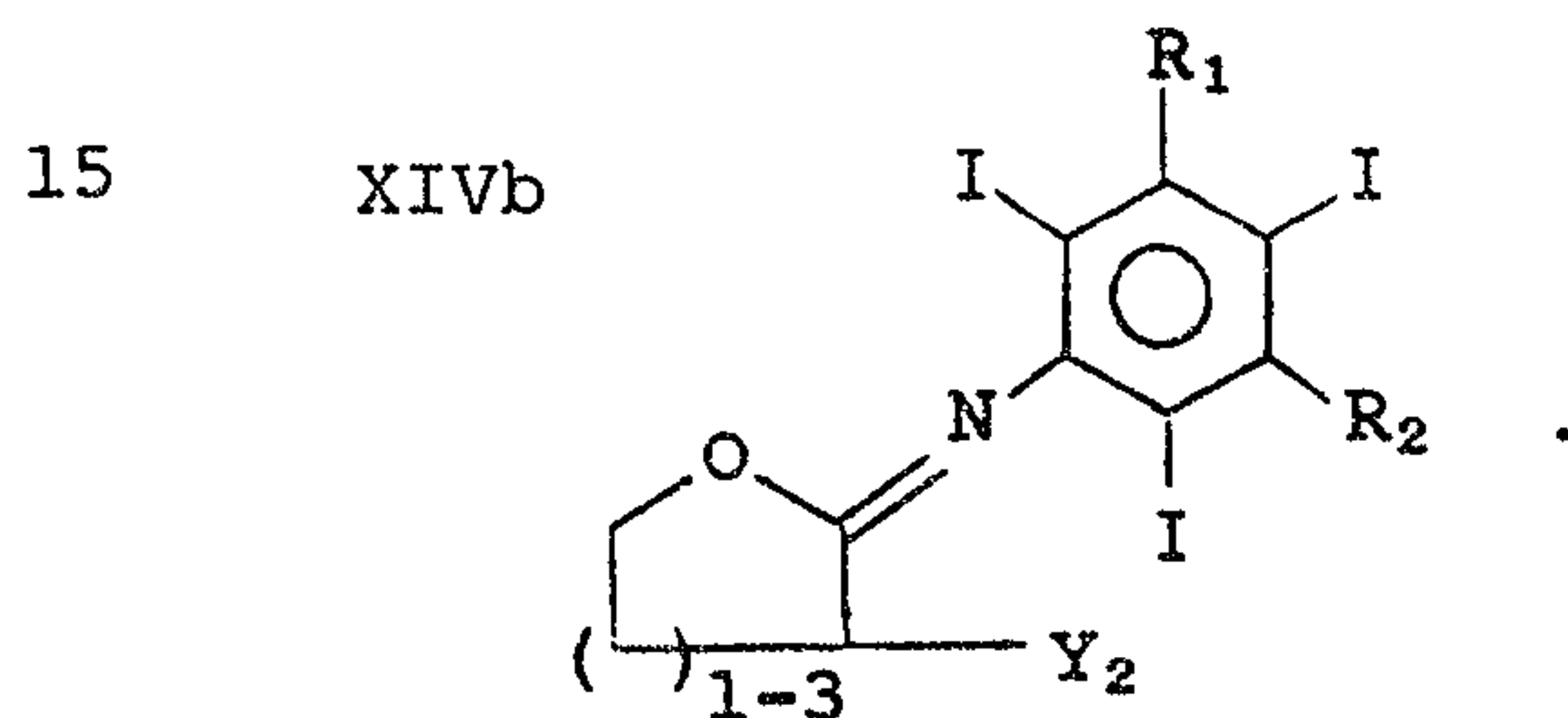
Compounds of formula XI can also be reacted with a compound of the formula



(where Y₁ and Y₂ are independently H or OH, L is a leaving group, e.g., Cl or Br)

10

in the presence of preferably a base or a Lewis acid catalyst to provide compounds of the formula

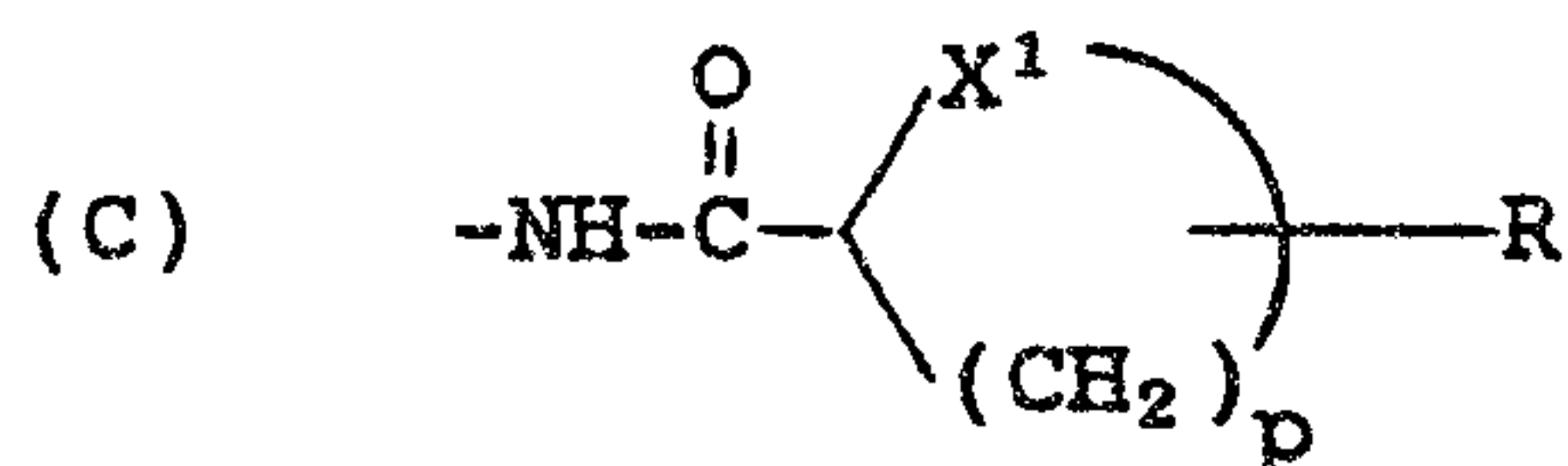


20

Most preferably the Lewis acid catalyst is AlCl₃ or SnCl₄.

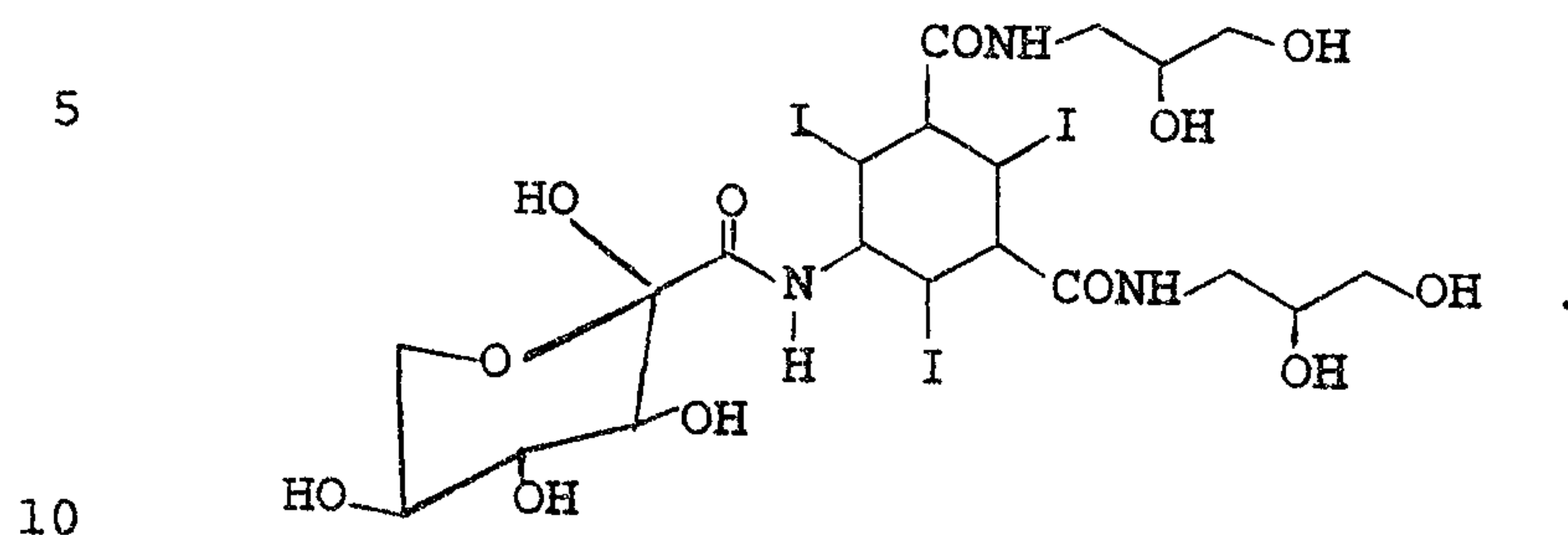
Examples of triiodinated phenyl compounds having the heterocyclic group

25

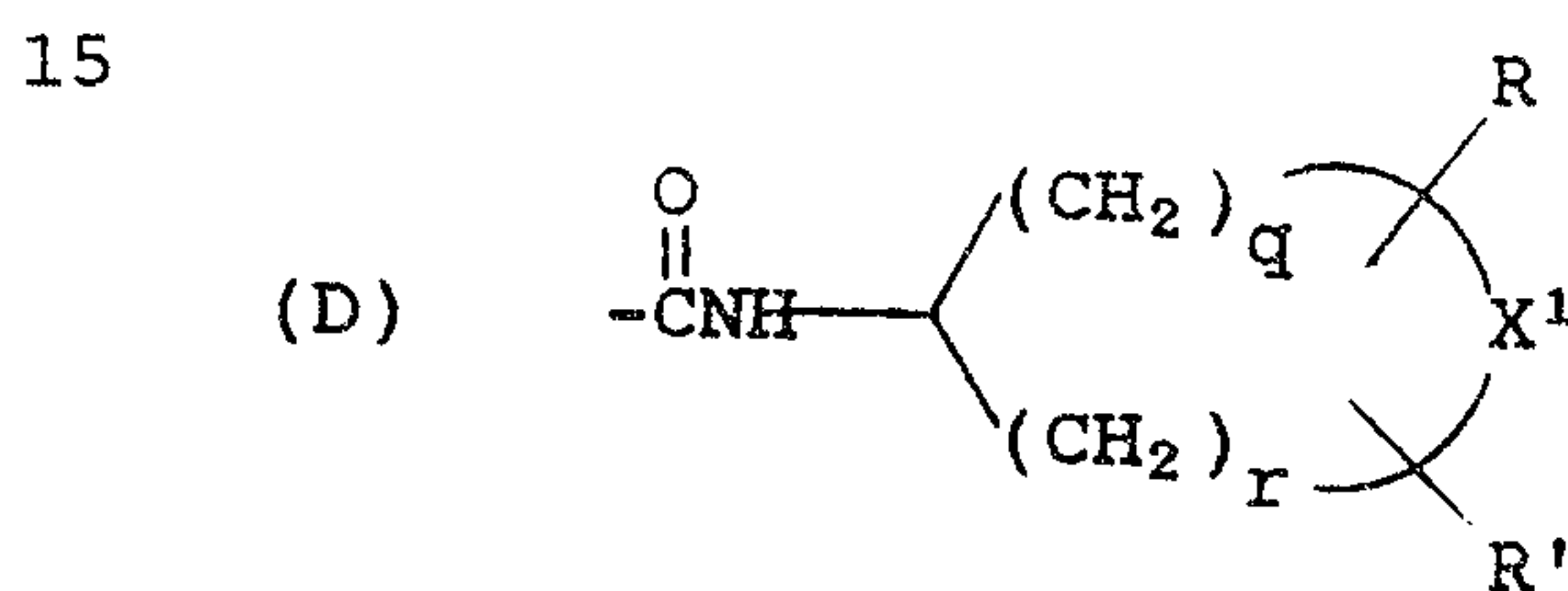


30 are known and have been disclosed for example by G. B. Hoey et al. in The Chemistry of X-Ray Contrast Media, Chapter 1, Radiocontrast Agents, Mr. Sovak (Ed.) Springer-Verlag, Berlin, 1984. A well

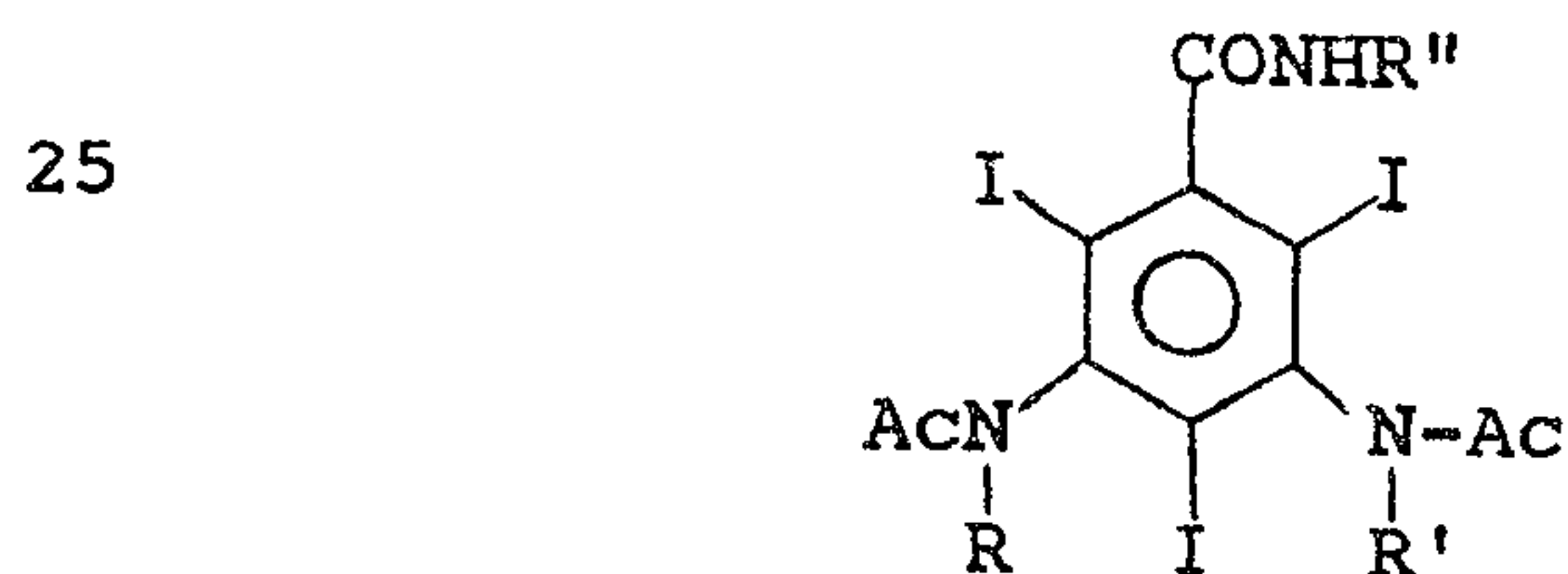
described example of this class is the compound
Iogalamide (MP-10013)



Examples of triiodinated phenyl compounds
having the heterocyclic group



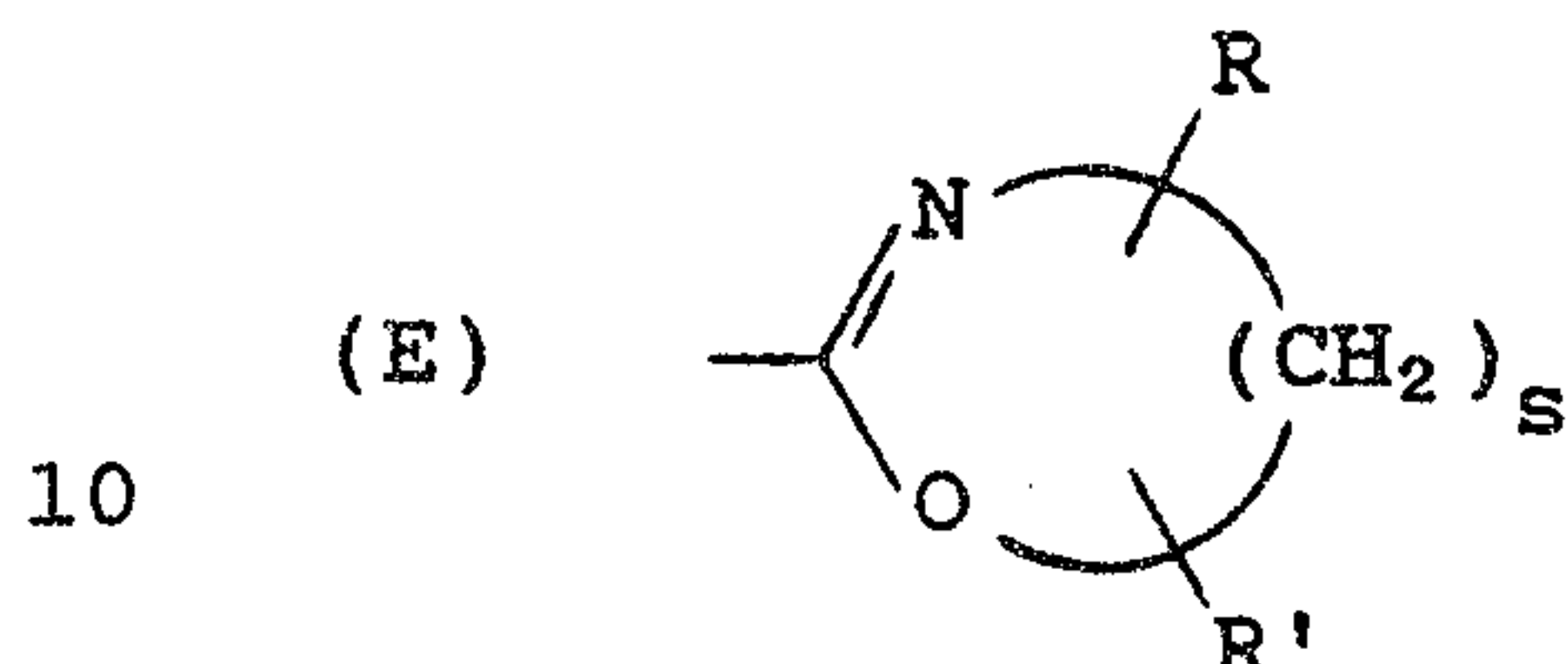
can be found in U. S. Patent 4,021,481 which
discloses compounds of the general formula



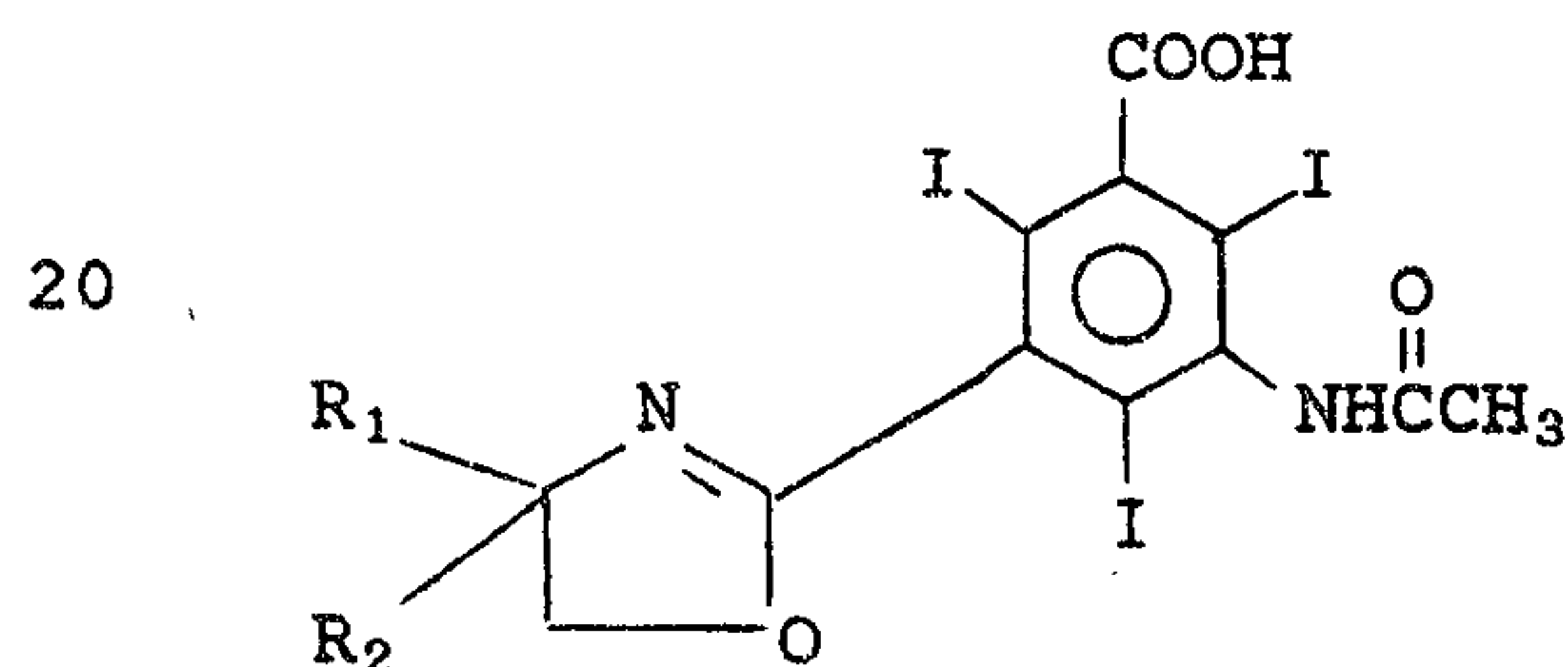
wherein R and R' are H, alkyl, or
hydroxyalkyl;

R" is alkyl, poly- or mono-hydroxyalkyl. A well known example of this class of compounds is metrizamide.

5 Examples of compounds having the heterocyclic group



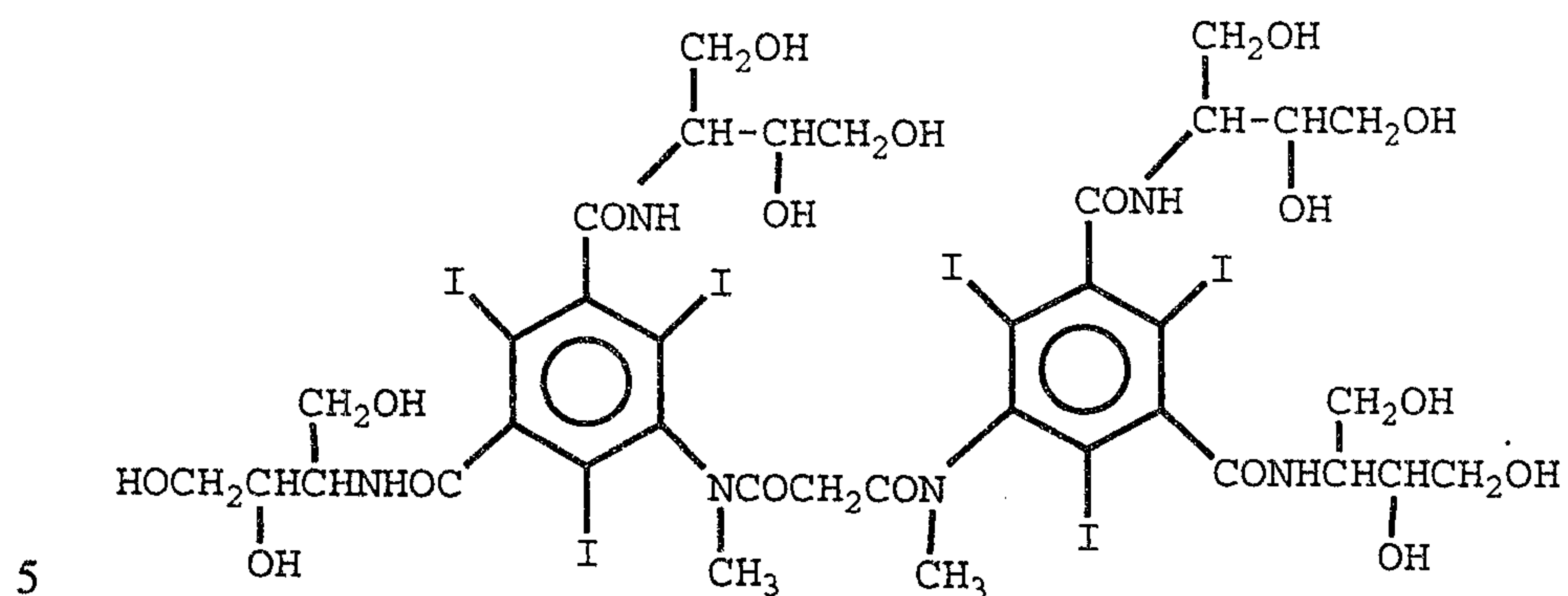
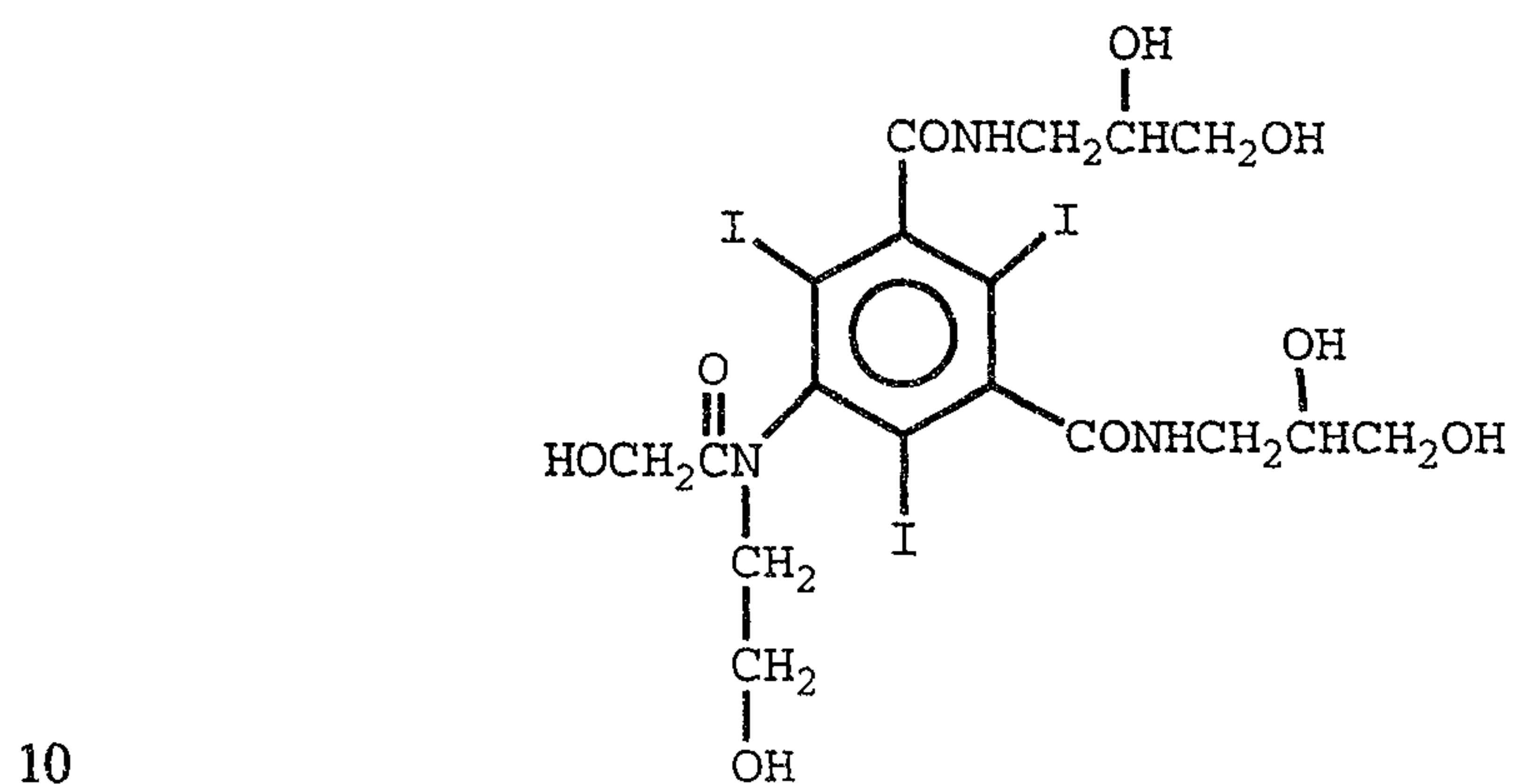
are also known and have been disclosed in U. S. Patent 4,066,743 to Kneller. The '743 patent
15 specifically discloses compounds (and preparation thereof) of the formula

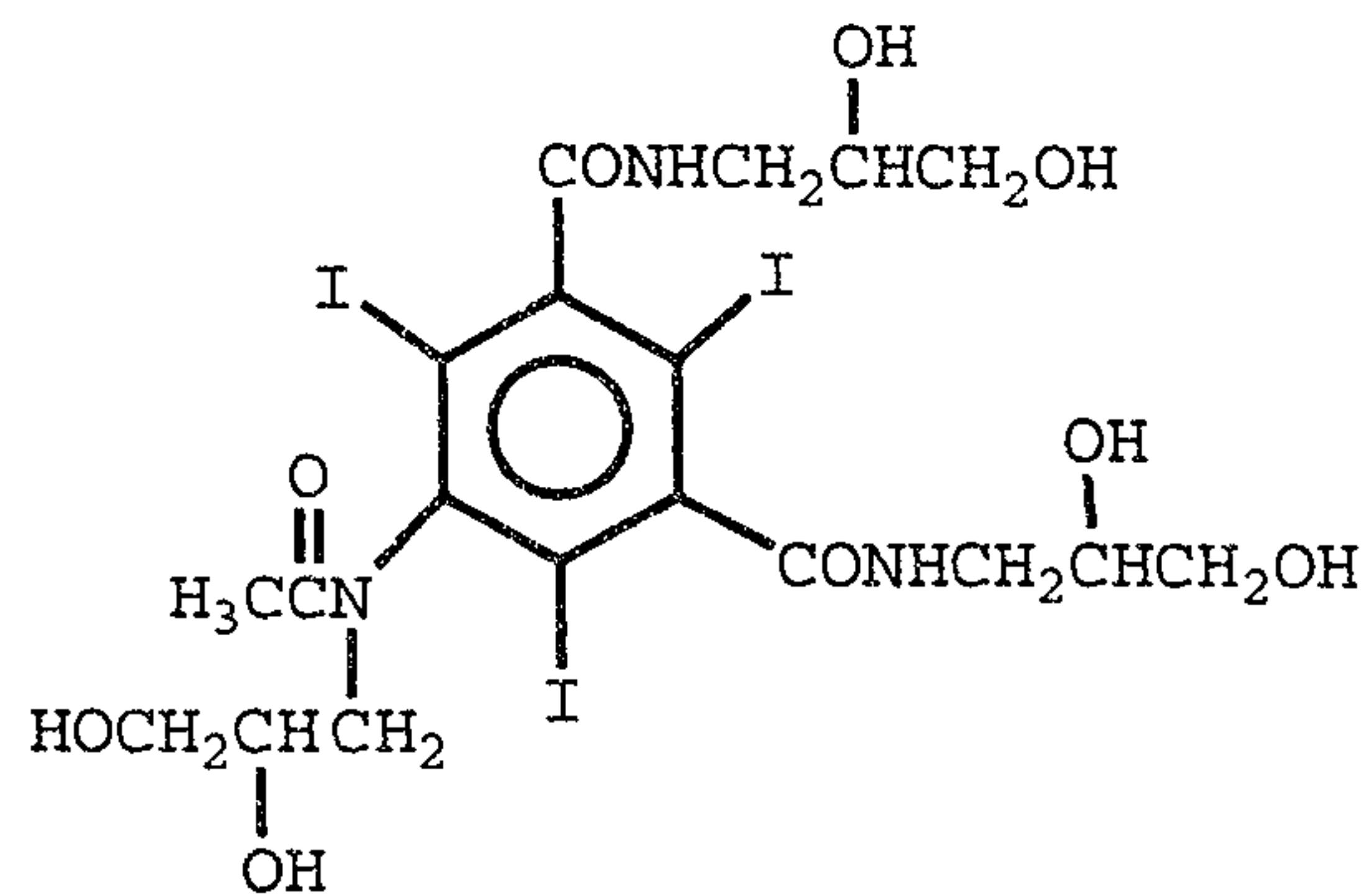
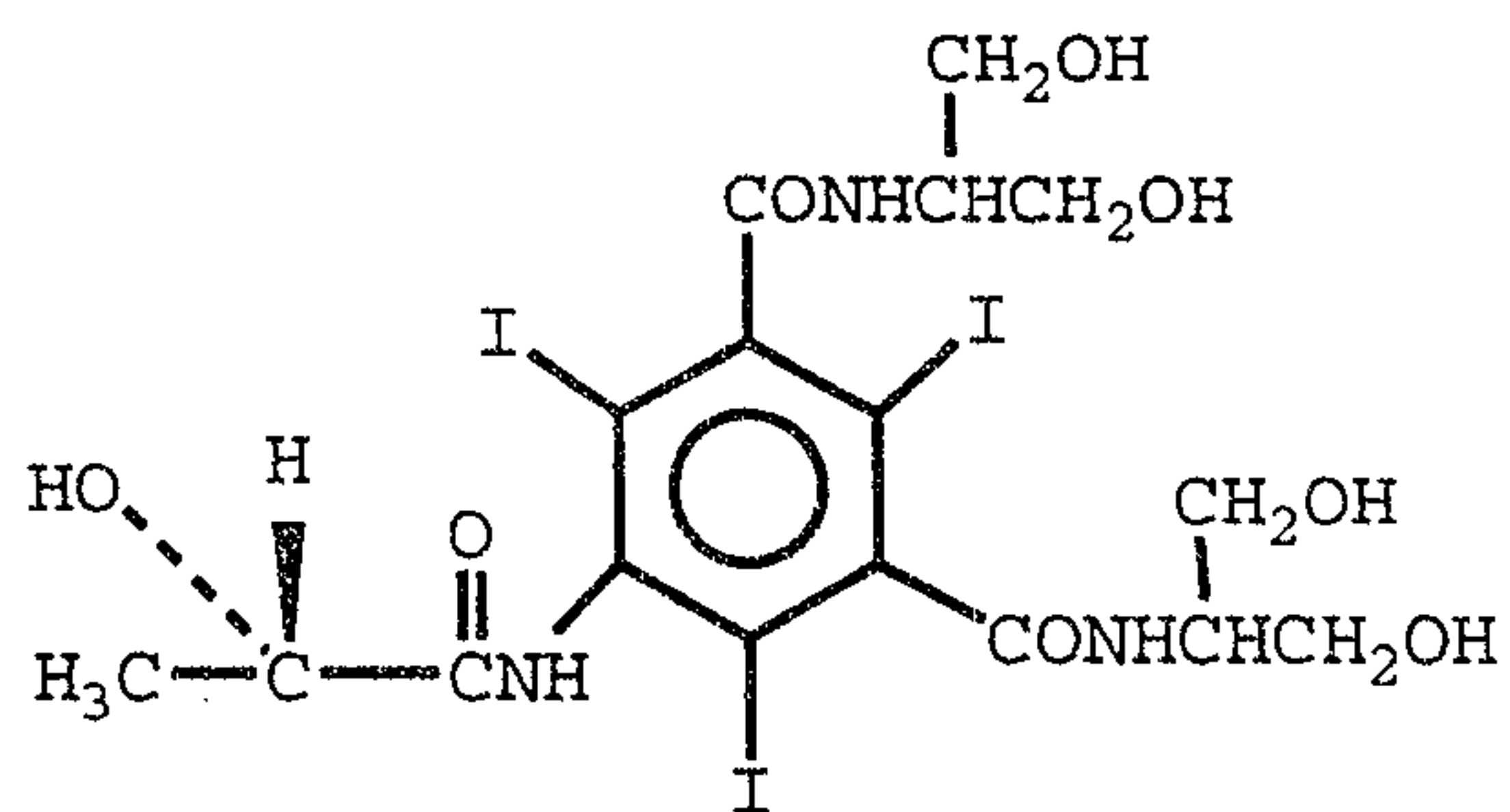


25 where R₁ is hydroxymethyl and R₂ is selected from hydroxymethyl or C₁₋₄ alkyl.

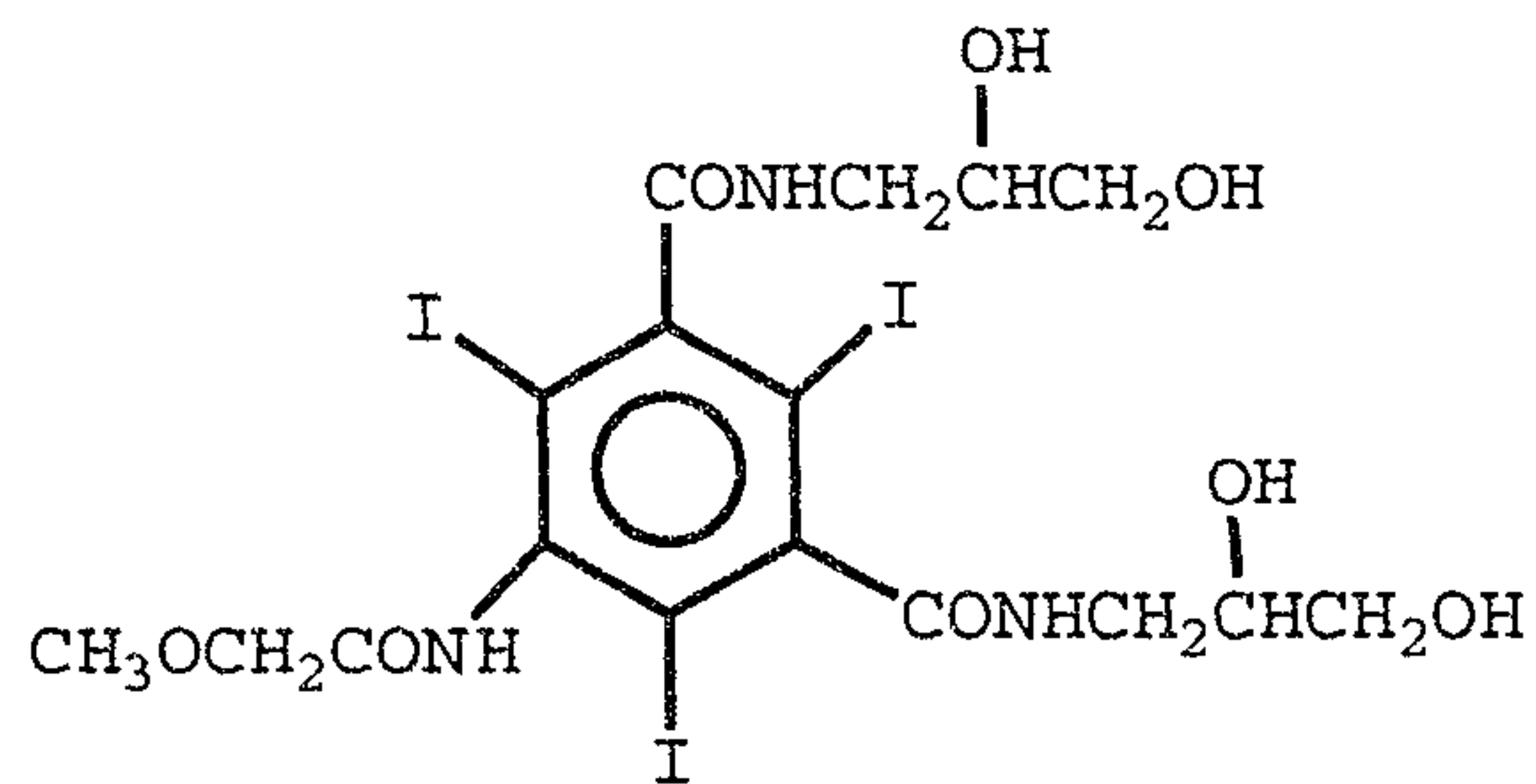
The dimers, wherein the linking group does not have heterocyclic moieties, are made by methods well described in prior art. Well-known examples
30 of dimers are Iotrolan and Ioxaglic acid.

A perusal of Table 1 reveals that all currently employed acyclic nonionic contrast agents, that we have studied, have APTT Index values in the range 0.2 to 0.3. On the other
5 hand, Metrizamide which is a heterocycle substituted Nonionic Iodinated Contrast Media (NICM) belonging to the class D, as per our definition, has an APTT Index value of 0.8. All the novel heterocycle substituted NICM candidates disclosed in this
10 patent, belonging to the classes A and B, have APTT Index values in the range 0.4-2.6. At least two of the new NICM have values greater than the ionic NICM, viz., ioxaglic acid and diatrizonic acid, which had values 0.9 and 1.0, respectively. Among
15 the heterocycles, those bearing branched hydroxymethyl substituents have values in the lower range of 0.3 to 0.5. The hydroxy substituted congeners have values in the middle range of 0.6 to 0.8 and the unsubstituted analogs have the highest values
20 in the range 2.0 to 2.6.

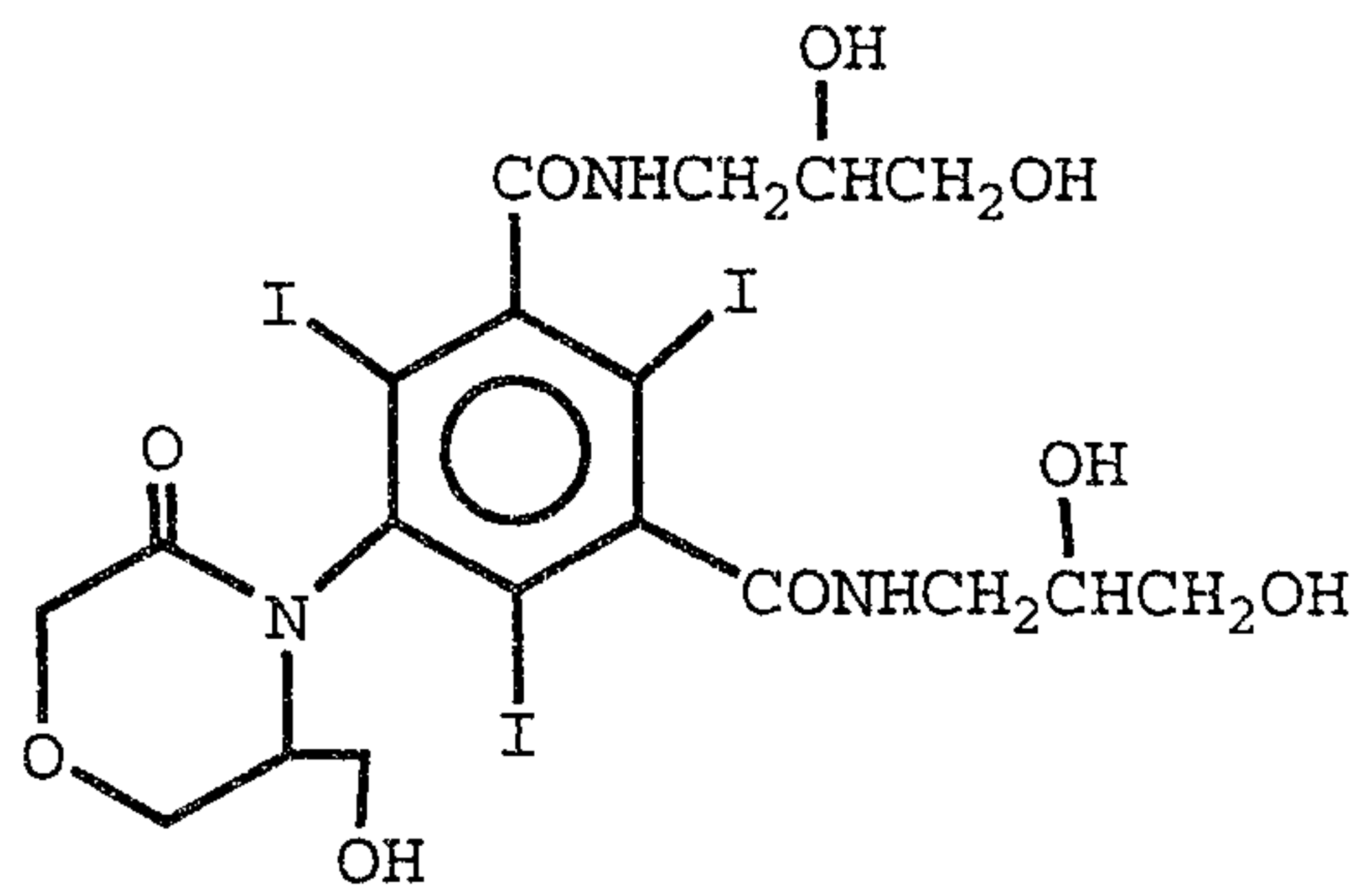
Structures for TABLE 1Isovist-240 (Iotrolan)Optirav-320 (Ioversol)

Omnipaque 350 (Iohexol)5 Isovue-370 (Iopamidol)Ultravist-370 (Iopromide)

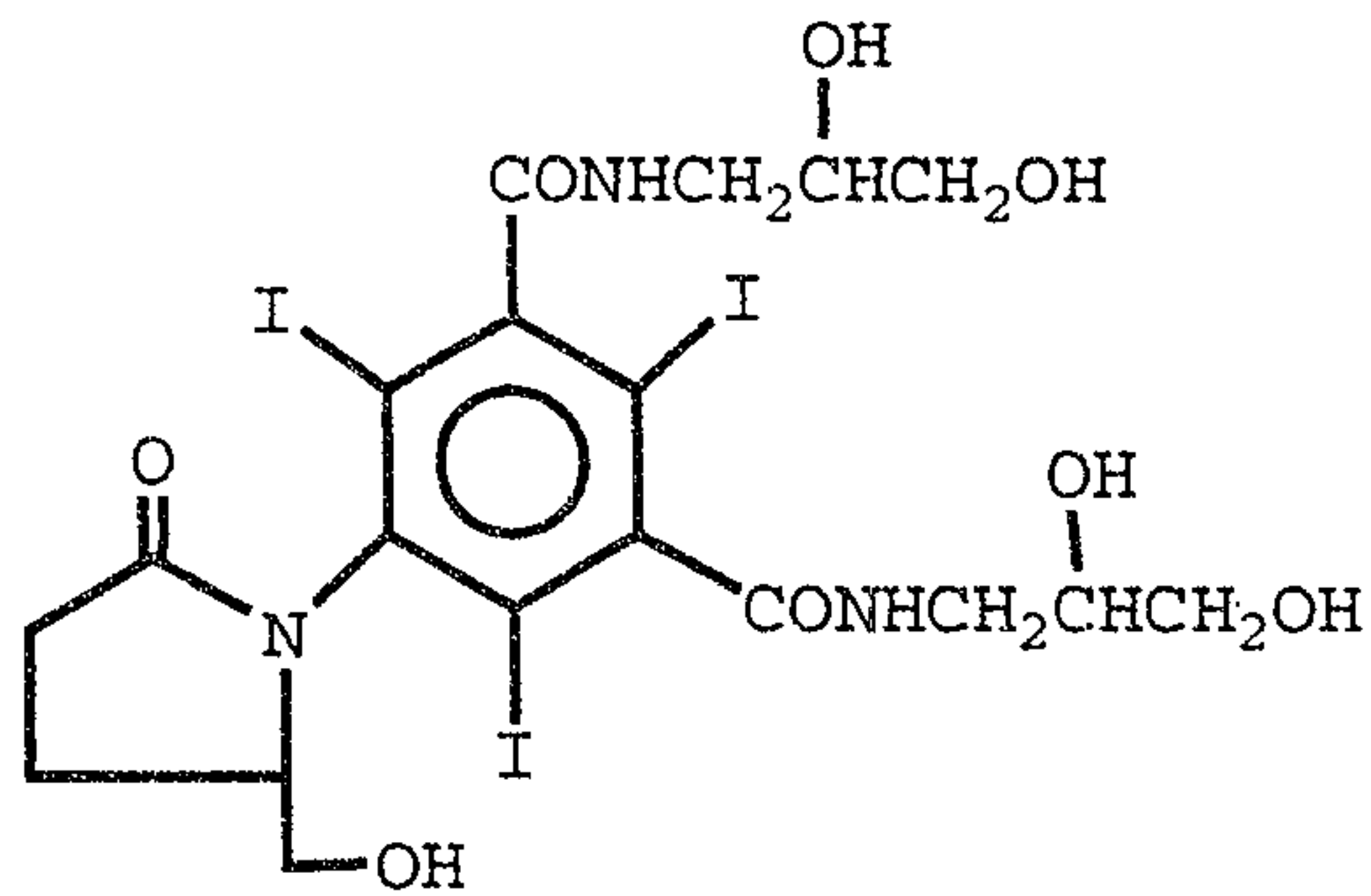
10



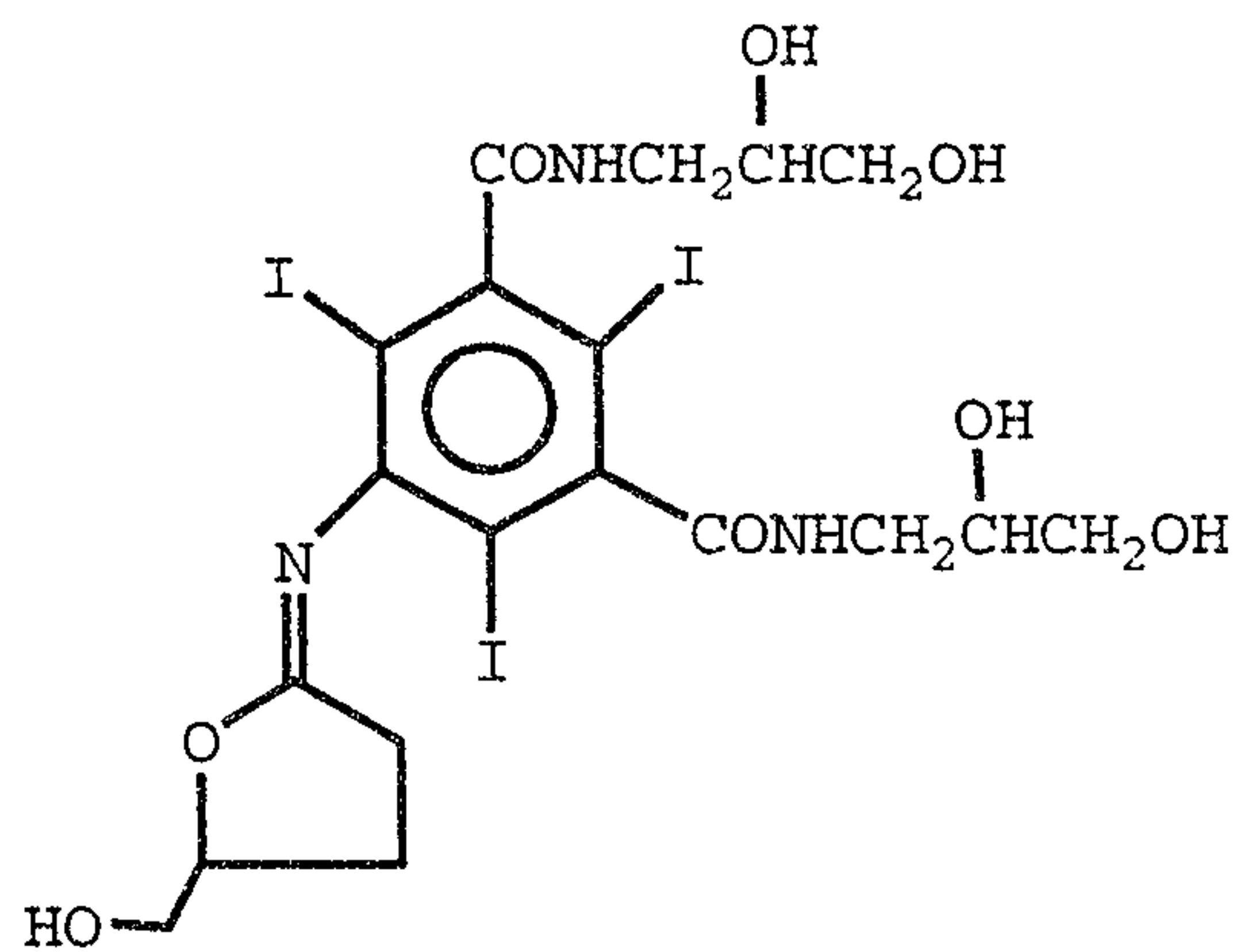
3HM5-Iomorhol-A

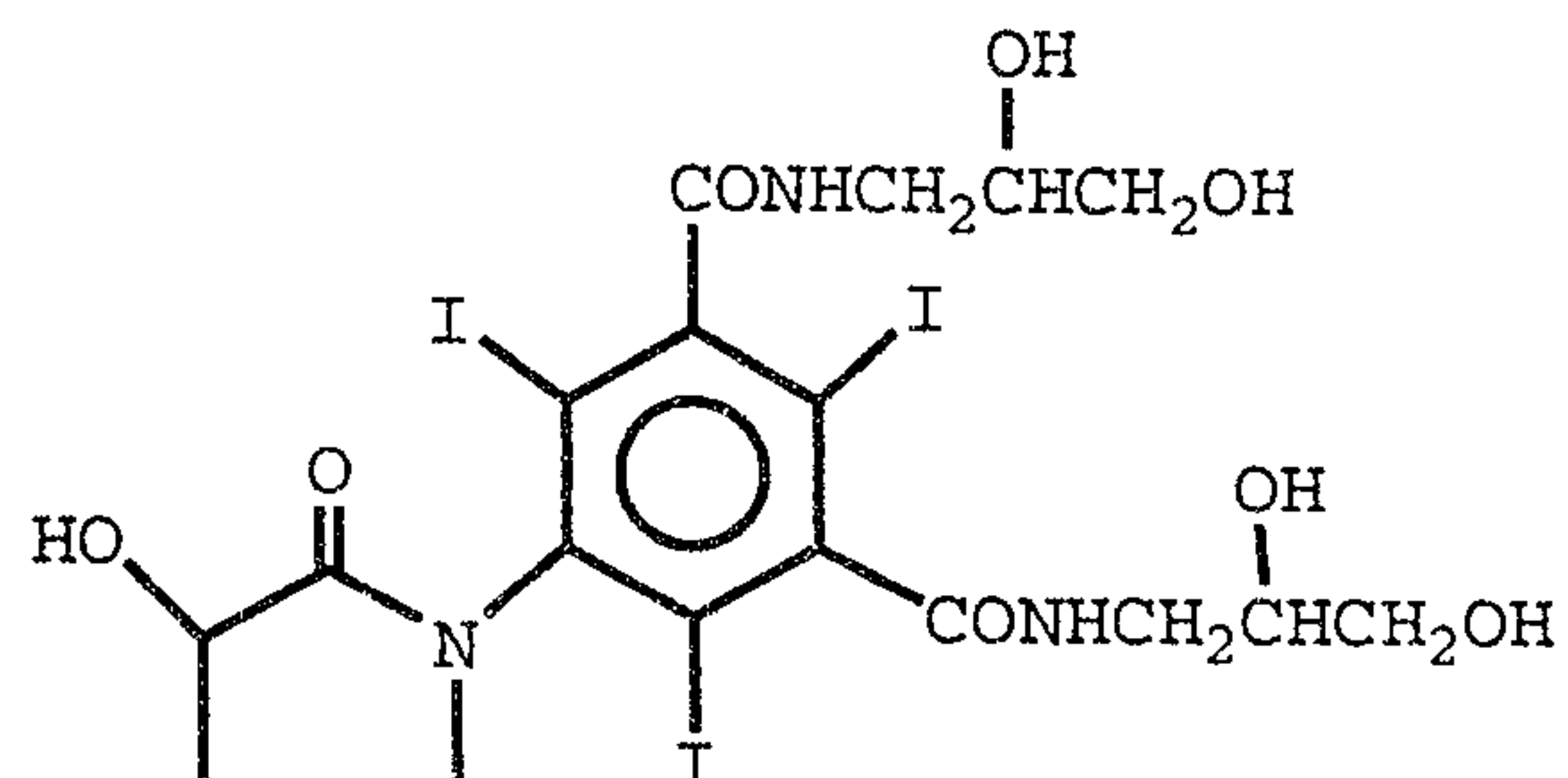
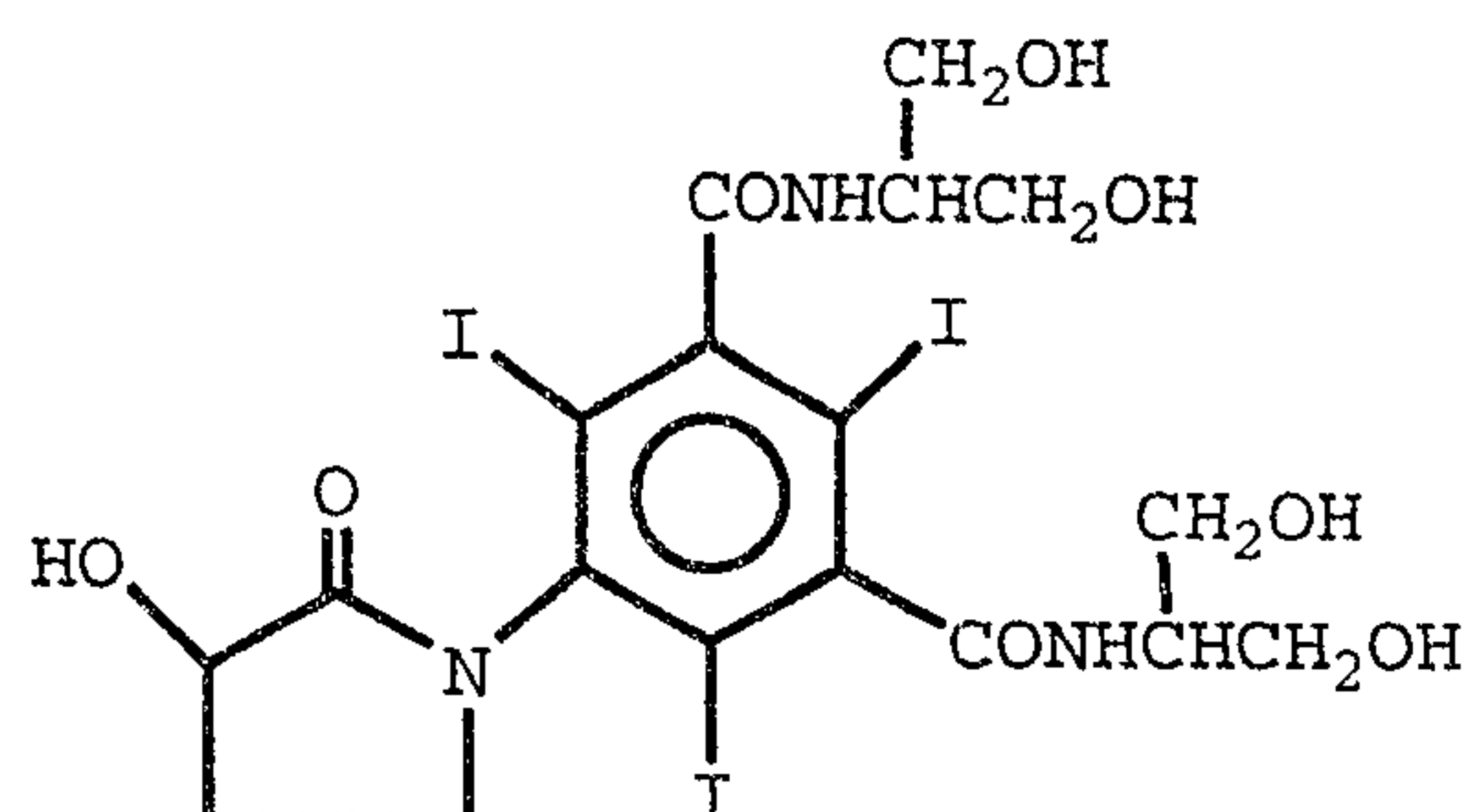


5 2HM5-Iopyrol-A

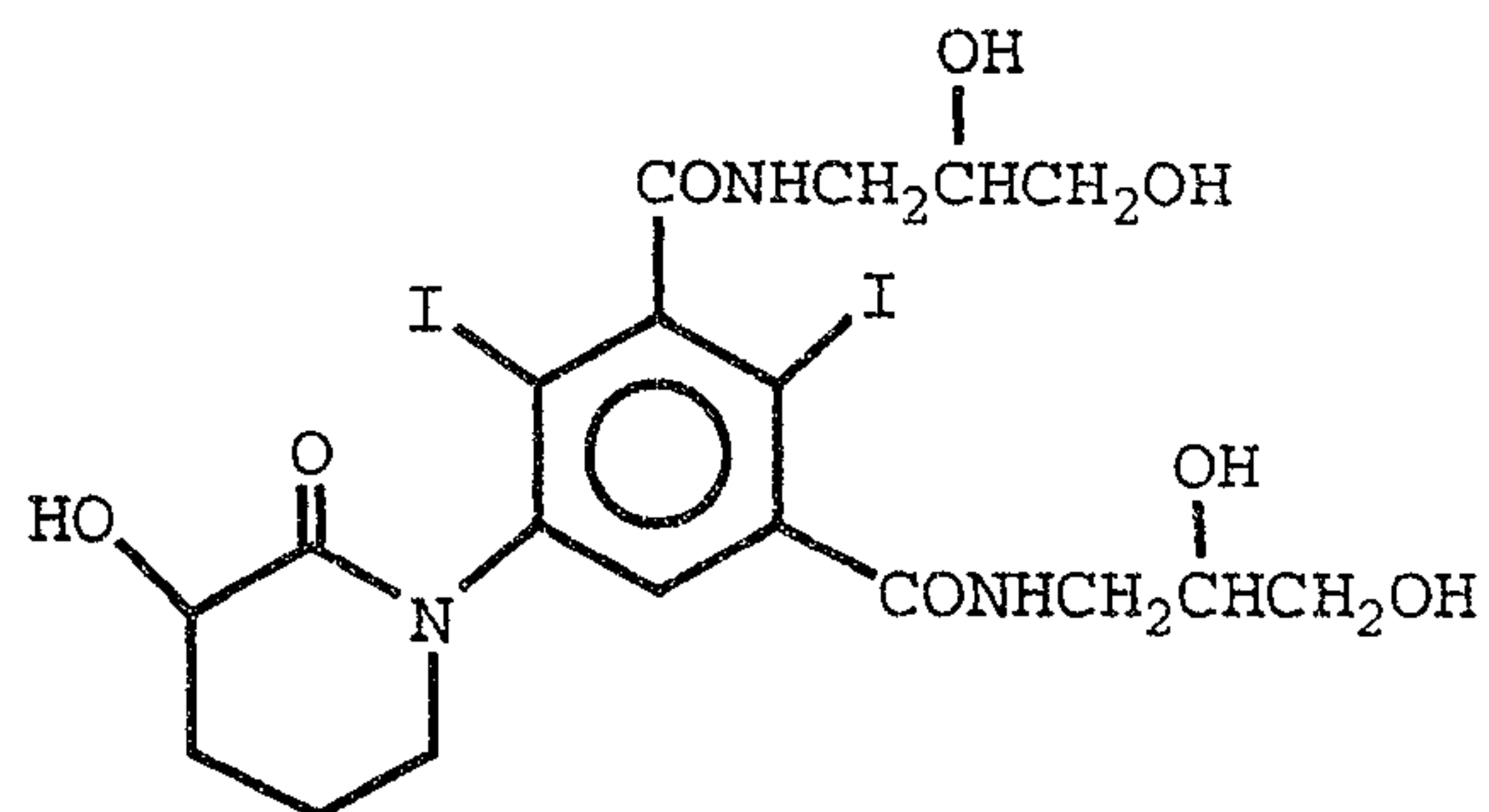


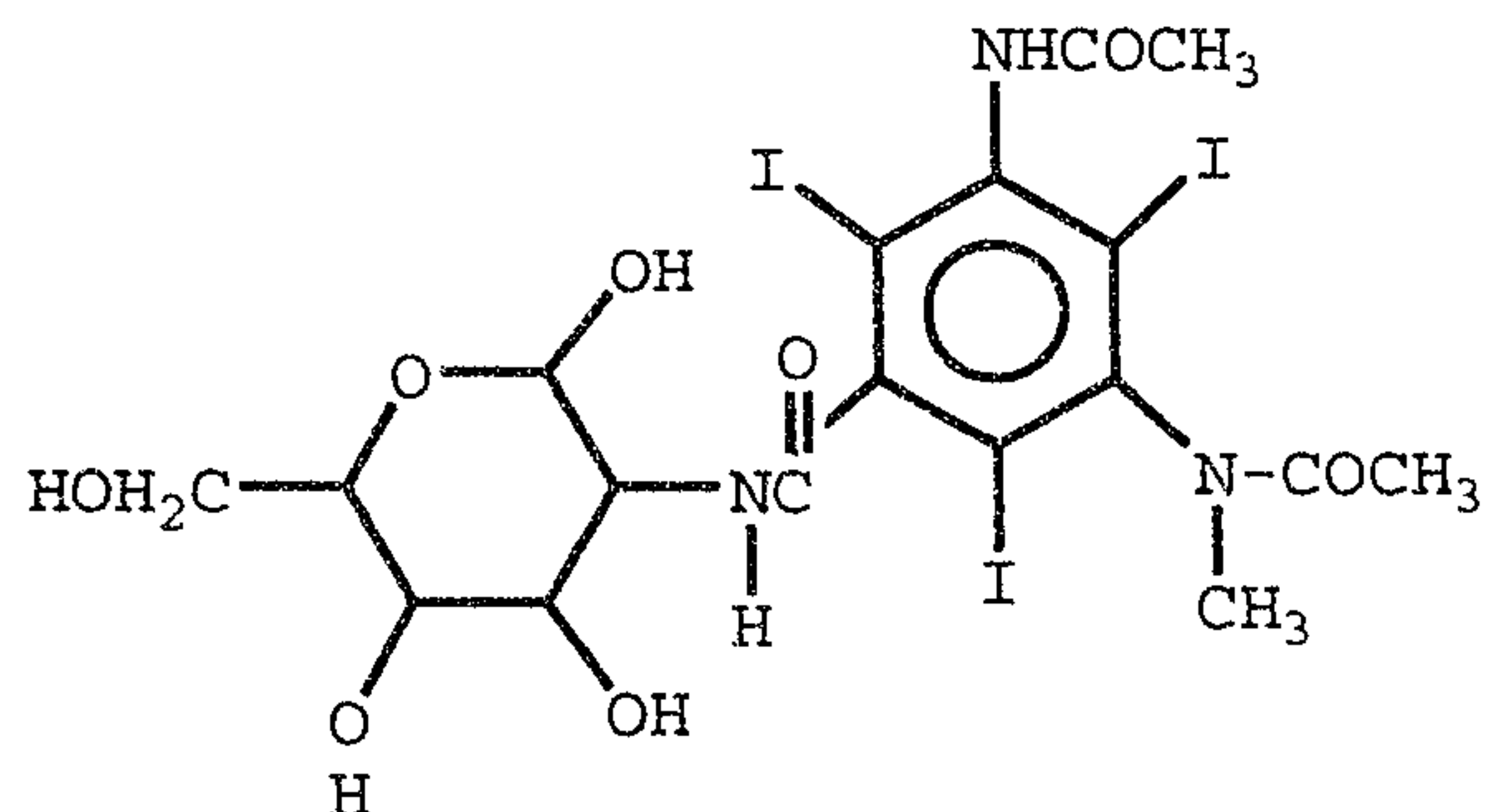
10 5HM-Iofurol-A



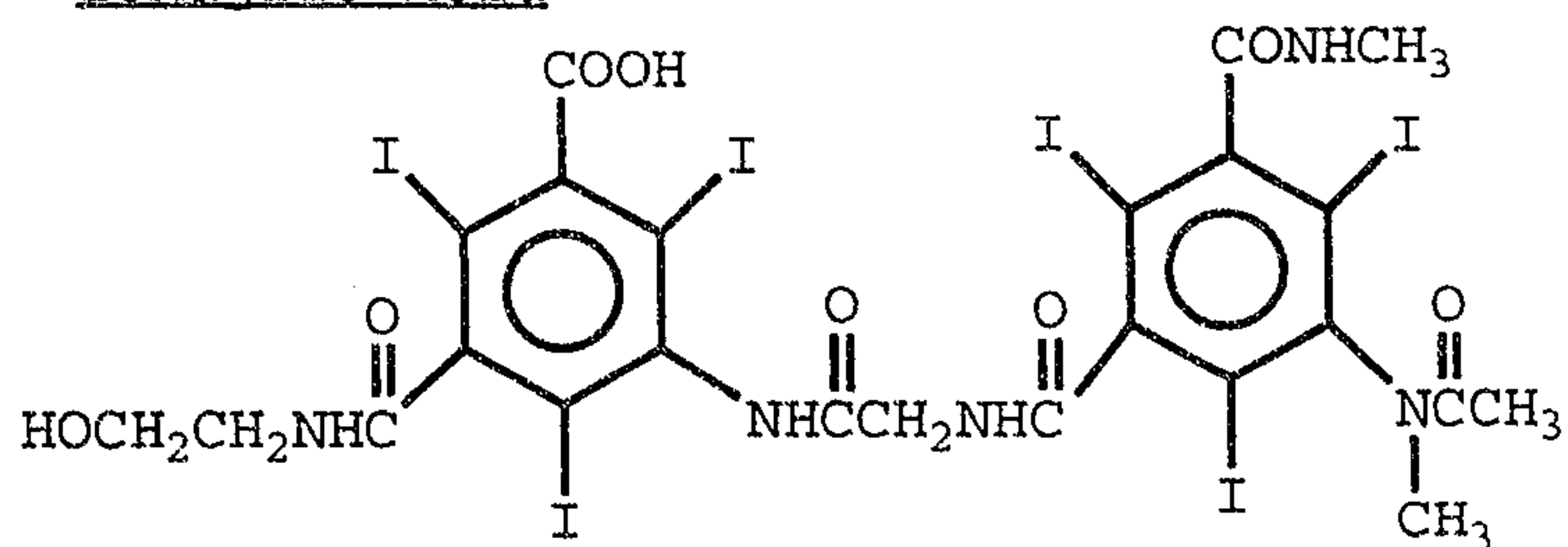
3H2-Iopyrol-A5 3H2-Iopyrol-S3H2-Iopiperidol-A

10



Metrizamide

5 Hexabrix-320 (Ioxaglic Acid/Ioxaglate Sodium/
Ioxaglate meglumine)

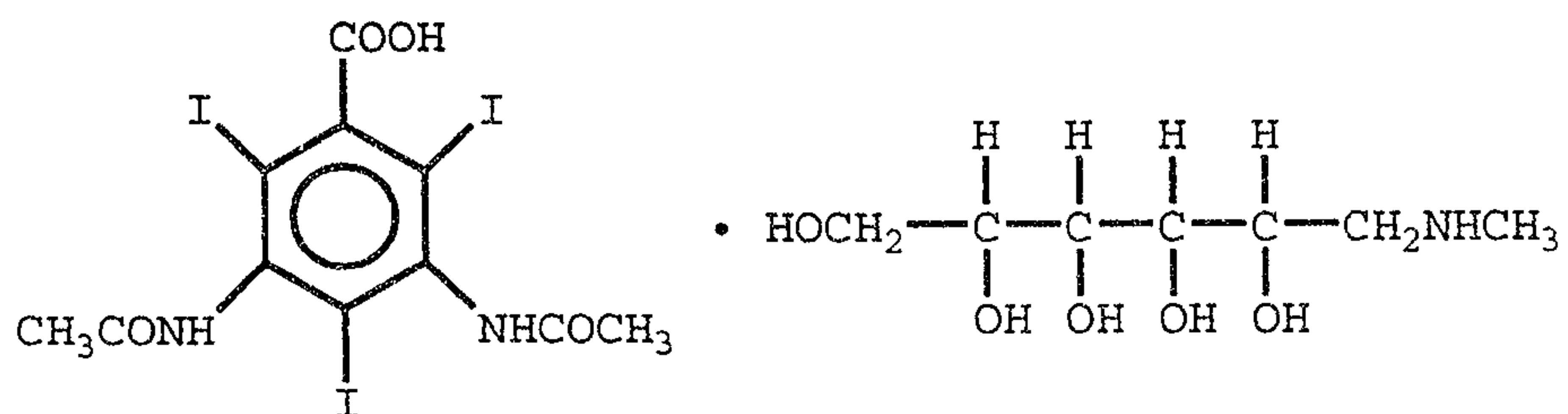
Ioxaglic Acid

10

in combination with the sodium and meglumine salts thereof.

Renografin-76 (Diatrozoate Meglumine)

15



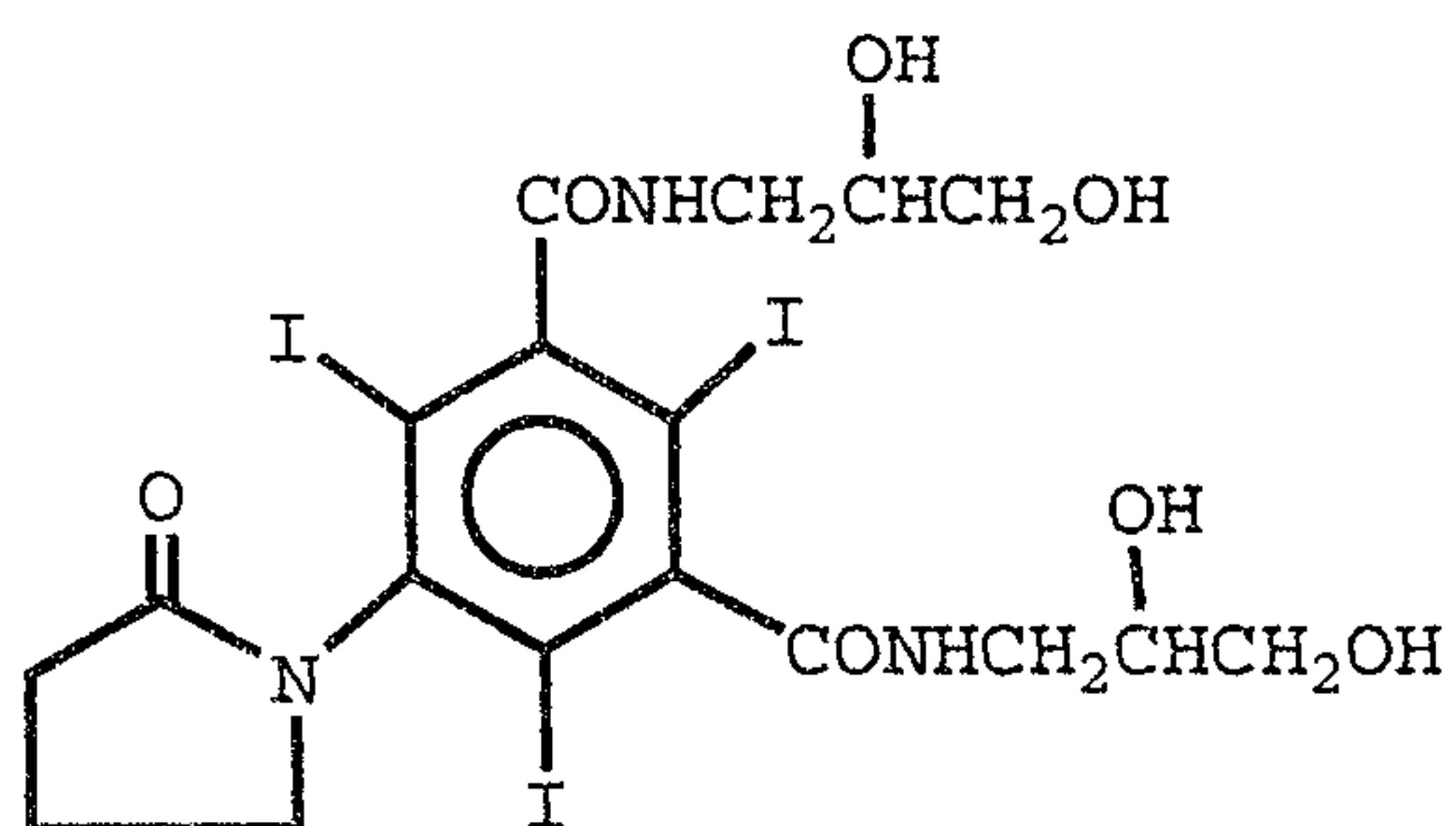
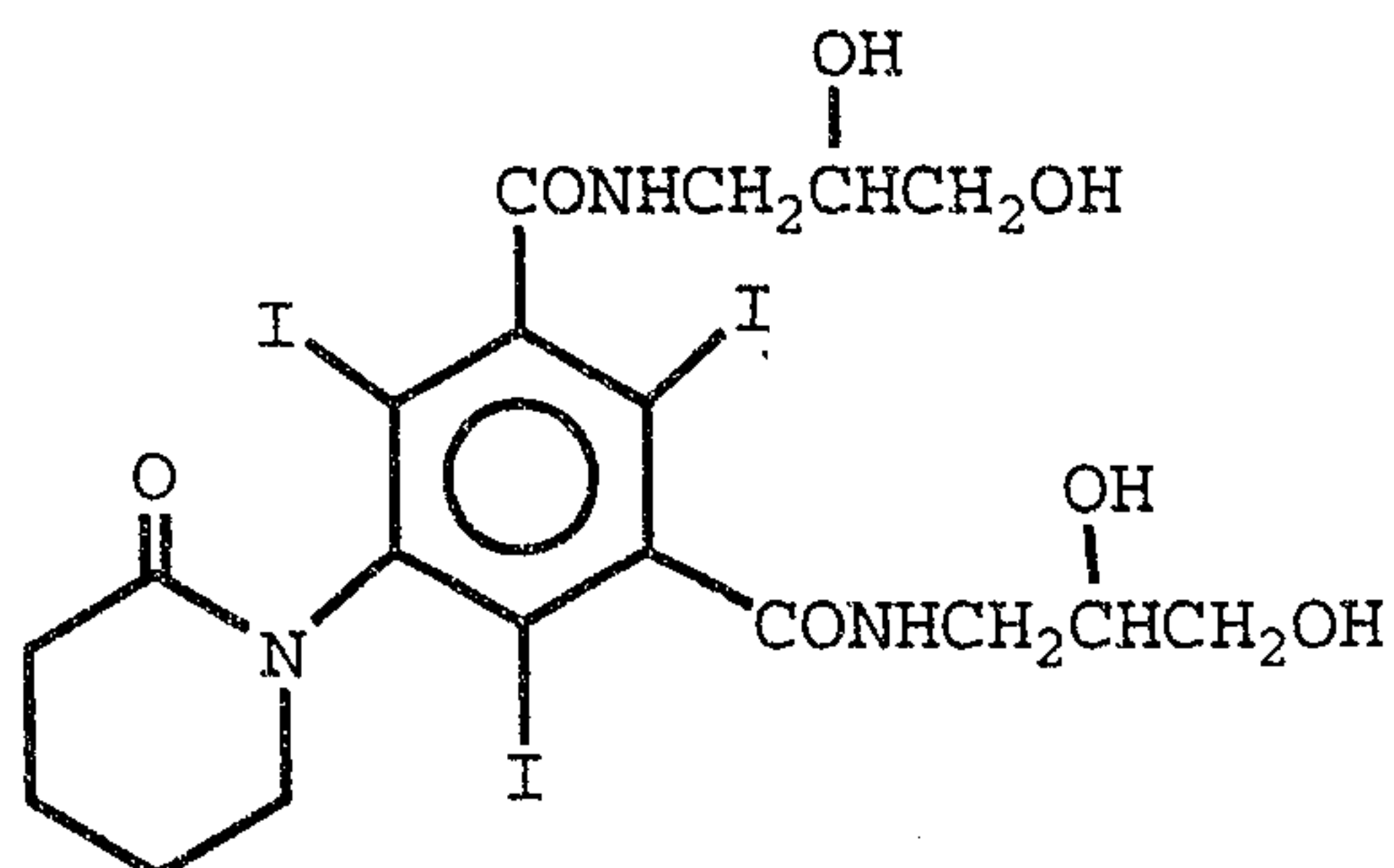
2-Iopyrol-A5 2-Iopiperidol-A

Table 1

APTT Index for Contrast Agents and the New
NICM Candidates¹

5	<u>Compound Name</u>	<u>Clotting Index (I)²</u>
	0.9% Saline TM	---
	Isovist-240 TM	0.2
10	Optiray-320 TM	0.3
	Ominpaque-350 TM	0.3
	Isovue-370 TM	0.3
	Ultravist-370 TM	0.3
	3HM5Iomorphol-A TM	0.4
15	2HM5-Iopyrol-A TM	0.4
	5HM-Iofurol-A TM	0.5
	3H2-Iopyrol-A TM	0.6
	3H2-Iopyrol-S TM	0.6
	3H2-Iopiperidol-A TM	0.8
20	Metrizamide TM	0.8
	Hexabrix-320 ^{TM3}	0.9
	Renografin-76 ^{TM3}	1.0
	2-Iopyrol-A TM	2.0
	2-Iopiperidol-A TM	2.6
25	¹ All measurements were carried out at a concentration of 370 mg I/mL, unless otherwise stated.	
	² $I = (T_c - T_s) / (T_r - T_s)$, where T_c is the clotting time for the substance, T_s is the clotting time for 0.9% saline, and T_r is the clotting time for	
30	Renografin-76 TM .	
	³ Ionic NICM.	

The compounds, compositions and methods of the invention are suitable for use in most fields of application in which water soluble radiopaque compounds are necessary, such as vasography, urography, arthrography, and for the visualization of body cavities containing cerebrospinal fluid. When formulated with addition agents which increase the viscosity of the aqueous solutions, the present compounds may be employed to advantage for bronchography and hysterosalpingography.

The radio-opaque compounds of formula XIX of the invention are particularly useful as active ingredients of aqueous compositions for visualization of the cardiovascular system, e.g., coronary angiography, and for cerebral angiography. Because of their non-ionic nature, they are suited for visualization of body cavities containing spinocerebral liquor such as in radiculography, ventriculography and myelography.

Aqueous compositions for the applications indicated above may be formulated to contain a single novel heterocyclic-containing compound of the present invention or prior art compounds otherwise disclosed herein, or more than one compound, if the individual compounds are very pure.

The radio-opaque compositions of the invention are aqueous solutions containing 15 g and more of the compounds per 100 ml, equivalent to 50 to approximately 500 mg iodine per ml. The more concentrated solutions are generally preferred, and they are applied in a manner generally known and selected according to the body

cavity which it is intended to visualize. In
vasography, the solutions are injected or infused
into the vessels, particularly the blood vessels.
Intravenous injection is resorted to in
5 urography. For myelography and radiculography,
the solutions are instilled after lumbar or
suoccipital puncture. The amounts of solution
necessary generally are 5 to 15 ml for
myelography, 3 to 5 ml for radiculography, and 1
10 to 2 ml for ventriculography.

Solutions or suspensions of the novel
contrast agents described herein may also be
administered enterally. For suspended solutions
1-100 millimoles of a contrast agent suspended in
15 1-2 liters of physiological compatible carrier
liquid is suitable.

The x-ray contrast compositions containing
the novel compounds of the invention as active
ingredients are prepared in a very simple manner
20 since no salt-forming or solubilizing ingredients
are needed. Any one of the novel compounds of the
examples may be dissolved under sterile conditions
in the desired amount of double-distilled water,
and the solution so obtained is ready to be
25 received in vials and sterilized. The compounds
are not decomposed at sterilizing temperatures
during the usual sterilizing periods (30 minutes
at 120°C or 60 minutes at 100°C).

The new heterocycle based non-ionic
30 contrast agents described herein have improved
features not present in currently available
contrast agents. Their superior stability
characteristic, eliminates the need to use organic

buffers or carbon dioxide saturation during sterilization of their formulations by autoclaving.

5 The new heterocycle based non-ionic contrast agents described herein are found to have excellent properties as to tolerance, stability, osmolality, viscosity and the like, factors important in angiography and urography.

10 Further, these novel heterocyclic non-ionic contrast agents of formula XIX, and all of the triiodinated phenyl compounds having heterocyclic groups (A), (B), (C), (D) or (E), including dimers thereof, are now believed to have anticoagulant properties equal to or greater than standard nonionic contrast agents such as iopamidol, 15 iohexol or ioversol and some of the new heterocyclic agents also have anti-coagulant properties equal to or greater than ionic contrast agents such as diatrizonic acid or ioxaglic acid. Thus, the methods, compositions and novel agents herein 20 provide reduced risk of clot formation in instances where clot formation is believed to be a problem.

The present application will be further illustrated by the following examples but should not be limited to the details described therein.

Example 1

5 [N,N'-Bis(2,3-dihydroxypropyl)-5-[[dihydro-5-(hydroxymethyl)-2(3H)-furanylidene]amino]-2,4,6-triiodo-1,3-benzenedicarboxamide

A. N,N'-Bis(2,3-bis(acetyloxy)propyl)-2,4,6-triiodo-5-[(1-oxo-4-pentenoyl)amino]-1,3-benzenedicarboxamide

10 4-Pentenoyl chloride (7.44 g, 62 mmol) was added to a stirred solution of 5-amino-N,N'-bis-[2,3-bis(acetyloxy)propyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (21.8 g, 25 mmol) in dimethylacetamide (150 mL) at room temperature and

15 the mixture was stirred for 16 hours. Dimethylacetamide was removed in vacuo and the residue dissolved in ethyl acetate (250 mL). The solution was washed with aqueous sodium bicarbonate (10%, 100 mL) and with water (2 x 100 mL). The organic

20 layer was dried and the solvent removed to obtain the crude product as an off-white solid. Further purification by crystallization from a mixture of ethyl acetate (250 mL) and hexane (50 mL) afforded the title A compound (21.3 g), m.p. 225-27°. TLC:

25 R_f 0.50 in ethyl acetate. Mass Spectrum: m/z 956 (M+H)⁺, 830, 653.

Elemental analysis calc'd for C₂₇H₃₂I₃N₃O₁₁:

C, 33.95; H, 3.38; I, 39.85; N, 4.40;
O, 18.42.

30 Found: C, 33.94; H, 3.24; I, 39.68; N, 4.30.

B. N,N'-Bis[2,3-bis(acetyloxy)propyl]-5-
[[dihydro-5-(iodomethyl)-2(3H)-furan-2-ylidene]amino]-2,4,6-triiodo-1,3-benzenedicarboxamide

5 To a solution of the title A compound (14.3 g, 15 mmol) in chloroform (300 mL), N-iodosuccinimide (4.48 g, 2 mmol) was added and the mixture heated at 50° for 1 hour. The progress of this reaction was monitored both by TLC and by reverse
10 phase HPLC. At the end of 1 hour the reaction was found to be complete. Chloroform was distilled off, the residue thus obtained dissolved in ethyl acetate (300 mL). The resulting solution was washed successively with water (100 mL), aqueous
15 sodium thiosulfate (25%, 2 x 50 mL), and water (2 x 100 mL). The organic layer was dried and the solvent removed to obtain the product as a light yellow glassy solid (16.6 g). This crude product was further purified by column chromatography over
20 silica gel (200 g, 45 cm column length) using ethyl acetate as eluent collecting 50 mL fractions. Fractions containing the pure product were combined and removal of the solvent afforded the title B compound as a glassy solid (13.0 g). TLC: R_f 0.47
25 in ethyl acetate. Mass Spectrum: m/z (M+H)⁺ 1082, 907, 781.

Elemental analysis calc'd for C₂₇H₃₁I₄N₃O₁₁:

C, 30.19; H, 2.94; I, 46.57; N, 3.86;
O, 16.44.

30 Found: C, 30.15; H, 2.77; I, 46.25; N, 3.72.

C. 5-[[5-[(Acetyloxy)methyl]dihydro-2-(3H)-
furanylidene]amino]-N,N'-bis(acetyloxy)-
propyl]-2,4,6-triiodo-1,3-benzenedicar-
boxamide

5 To a solution of the title B compound
(16.32 g, 150 mmol) in glacial acetic acid (165
mL), was added silver acetate (10.01 g, 600 mmol),
and the mixture stirred at 80° for 16 hours. The
insoluble materials were filtered off, acetic acid
10 removed in vacuo at 60°, the residue dissolved in
ethyl acetate (200 mL), and the resulting solution
washed successively with water (100 mL), aqueous
sodium bicarbonate (200 mL) and water (100 mL).
The ethyl acetate layer was dried and removal of
15 the solvent afforded the crude product as a red
colored solid. Purification by column chromatography
over silica gel using a solvent gradient varying
from 25% hexane in ethyl acetate to 10% hexane in
ethyl acetate afforded pure title C compound as a
20 light pink glassy solid (13.2 g). TLC: R_f 0.35 in
ethyl acetate. Mass Spectrum: m/z $(M+H)^+$ 1014,
888, 839, 713.

Elemental analysis calc'd for $C_{29}H_{34}I_3N_3O_{13}$:

25 C, 34.37; H, 3.38; I, 37.57; N, 4.15;
O, 20.53;

Found: C, 34.37; H, 3.53; I, 37.88; N, 4.17.

D. [N,N'-Bis(2,3-dihydroxypropyl)-5-[[dihydro-
5-(hydroxymethyl)-2(3H)-furanylidene]amino]-
30 2,4,6-triiodo-1,3-benzenedicarboxamide

A solution of the title C compound (22.3 g,
22 mmol) in methanol (150 mL) was treated with
sodium methoxide (23 mmol) in methanol (16 mL) and

RA58

-39-

the mixture was stirred at room temperature for 3 hours. At the end of this time, the pH of the solution was adjusted to 6 with the ion exchange resin Dowex-50™(H)⁺. The resin was filtered off, the methanol removed in vacuo and the residue, thus obtained, dissolved in water (150 mL) and then treated three times with decolorizing charcoal (3 x 1 g), filtered and the solvent removed to obtain the crude product as a beige glassy solid (17.50 g). HPLC analysis showed the purity of this material to be 97.7%. This product (17.50 g) was further purified by reverse phase column chromatography, using the nonionic CHP-20™ resin using aqueous ethanol as eluent. The desired product was obtained as a colorless glassy solid (15.95 g). 1.00 g of this material was crystallized from hot butanol (30 mL) to afford the title compound (970 mg) as colorless needles. TLC: R_f 0.3 in ethyl acetate/methanol (7:3). Mass Spectrum: m/z (M+H)⁺ 804, 713, 587.

Elemental analysis calc'd for C₁₉H₂₄I₃N₃O₃·0.85H₂O:
C, 27.88; H, 3.16; I, 46.52; N, 5.14;
O, 15.64;
Found: C, 28.03; H, 2.99; I, 46.35; N, 4.92;
H₂O, 1.87.

Example 2

5-[[Dihydro-5-(hydroxymethyl)-2(3H)-furanylidene]-
amino]-N,N'-bis[(2-hydroxy)-1-(hydroxymethyl)-
5 ethyl]-2,4,6-triiodo-1,3-benzenedicarboxamide

A. N,N'-Bis[2-(acetyloxy)-1-[(acetyloxy)-
methyl]ethyl]-2,4,6-triiodo-5-[(1-oxo-4-
pentenyl)amino]-1,3-benzenedicarboxamide
10 4-Pentenoyl chloride (11.9 g, 100 mmol) was
added to a stirred solution of N,N'-bis-[2-
(acetyloxy)-1-[(acetyloxy)-methyl]ethyl]-5-amino-
2,4,6-triiodo-1,3-benzenedicarboxamide (47.75 g,
50 mmol) in dimethylacetamide (400 mL) at room
15 temperature and the mixture was stirred for 16
hours. Dimethylacetamide was removed in vacuo and
the residue dissolved in ethyl acetate (600 ml).
The solution was washed with aqueous sodium
bicarbonate (10%, 2 x 150 mL) and with water (2 x
20 100 mL) and brine (150 mL). The organic layer
was dried and the solvent removed to obtain the
crude product as an off-white solid. Further
purification by crystallization from a mixture of
acetone (250 mL) and hexane (75 mL) afforded the
25 title A compound (42.5 g), m.p. 162-64°. TLC: R_f
0.55 in ethyl acetate. Mass Spectrum: m/z 956
(M+H)⁺, 830, 653.

Elemental Analysis calc'd for C₂₇H₃₂I₃N₃O₁₁:
C, 33.95; H, 3.38; N, 4.40; I, 39.85;
30 Found: C, 33.93; H, 3.18; N, 4.22; I, 39.84.

B. N,N'-Bis[2-(acetyloxy)-1-[(acetyloxy)-methyl]ethyl]-5-[[dihydro-5-(iodomethyl)-2(3H)-furanylidene]amino]-2,4,6-triiodo-1,3-benzenedicarboxamide

5 To a solution of the title A compound (9.55 g, 10 mmol) in chloroform (200 mL), N-iodosuccinimide (4.48 g, 20 mmol) was added and the mixture heated at 50° for 1 hour. The progress of this reaction was monitored both by TLC and by reverse
10 phase HPLC. At the end of 1 hour, the reaction was found to be complete. Chloroform was distilled off, the residue thus obtained dissolved in ethyl acetate (200 mL) and the resulting solution washed successively with water (100 mL), aqueous sodium
15 thiosulfate (25%, 2 x 50 mL), and water (2 x 100 mL). The organic layer was dried and the solvent removed to obtain the product as a light yellow glassy solid (10.2 g). This crude product was further purified by column chromatography over
20 silica gel (200 g) using a mixture of ethyl acetate and hexane (7:3) as eluent to obtain the title B compound as a glassy solid (8.5 g), m.p. 126-30° (froaths), 145-50° (decomposes).

Elemental analysis calc'd for C₂₇H₃₁I₄N₃O₁₁:

25 C, 29.99; H, 2.91; N, 3.89; I, 46.95;

Found: C, 30.04; H, 2.81; N, 3.77; I, 47.05.

C. N,N'-Bis[2-(acetyloxy)-1-[(acetyloxy)-methyl]ethyl]-5-[[5-[acetyloxy)methyl]-dihydro-2-(3H)-furanylidene]amino]-2,4,6-triiodo-1,3-benzenedicarboxamide

30 To a solution of the title B compound (7.5 g, 6.93 mmol) in glacial acetic acid (100

RA58

-42-

mL), was added silver acetate (3.34 g, 20 mmol), and the mixture stirred at 80° for 16 hours. The insoluble materials were filtered off, acetic acid removed in vacuo at 60°, the residue dissolved in
5 ethyl acetate (250 mL), and the resulting solution washed successively with water (100 mL), aqueous sodium bicarbonate (100 mL) and water (100 mL). The ethyl acetate layer was dried and removal of the solvent afforded the crude product as a red
10 colored solid. The crude material was chromatographed over silica gel (200 g, 250 cm column length) eluting with a solvent gradient varying from 25% hexane in ethyl acetate to 10% hexane in ethyl acetate to obtain the title C compound as a
15 pink glassy solid (5.5 g), m.p. 172-75°.

Elemental analysis calc'd for C₂₉H₃₄I₃N₃O₁₃:

C, 34.37; H, 3.38; N, 4.15; I, 37.57;

Found: C, 34.22; H, 3.50; N, 4.06; I, 37.82.

20 D. 5-[[Dihydro-5-(hydroxymethyl)-2(3H)-furanlylidene]amino]-N,N'-bis[(2-hydroxy)-1-(hydroxymethyl)ethyl]-2,4,6-triiodo-1,3-benzenedicarboxamide

A solution of the title C compound (2.7 g, 2.66 mmol) in methanol (50 mL) was treated with
25 sodium methoxide (2.6 mmol) in methanol (6 mL) and the mixture was stirred at room temperature for 3 hours. At the end of this time, the pH of the solution was adjusted to 6 with the ion exchange
30 resin Dowex-50™-(H)⁺. The resin was filtered off, the methanol removed in vacuo and the residue, thus obtained, dissolved in water (150 ml) and then treated three times with decolorizing charcoal

RA58

-43-

(0.3 g), filtered and the solvent removed to obtain a beige glassy solid (2.1 g). This product was further purified by reverse phase column chromatography, using the nonionic CHP-20™ resin and
5 aqueous ethanol as eluant to obtain the pure title compound (1.85 g), m.p. 208-10° (softens), 258-62° (froths), 285-89° (decomposes).

Elemental analysis calc'd for $C_{19}H_{24}N_3I_3O_8 \cdot 0.6 H_2O$:

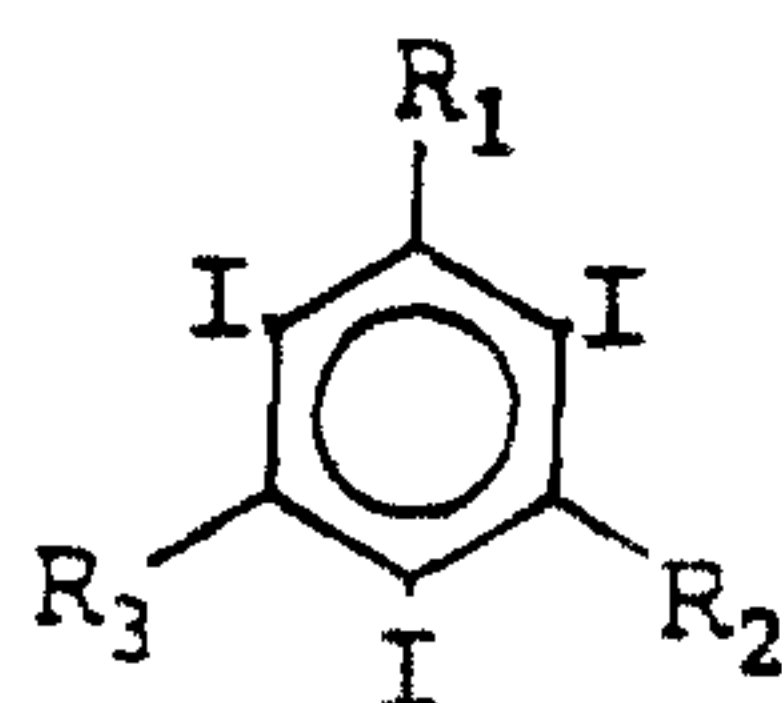
C, 28.04; H, 3.12; N, 5.16; I, 46.58;

10 Found: C, 28.15; H, 3.28; N, 5.21; I, 46.78;
H₂O, 1.32.

- 44 -

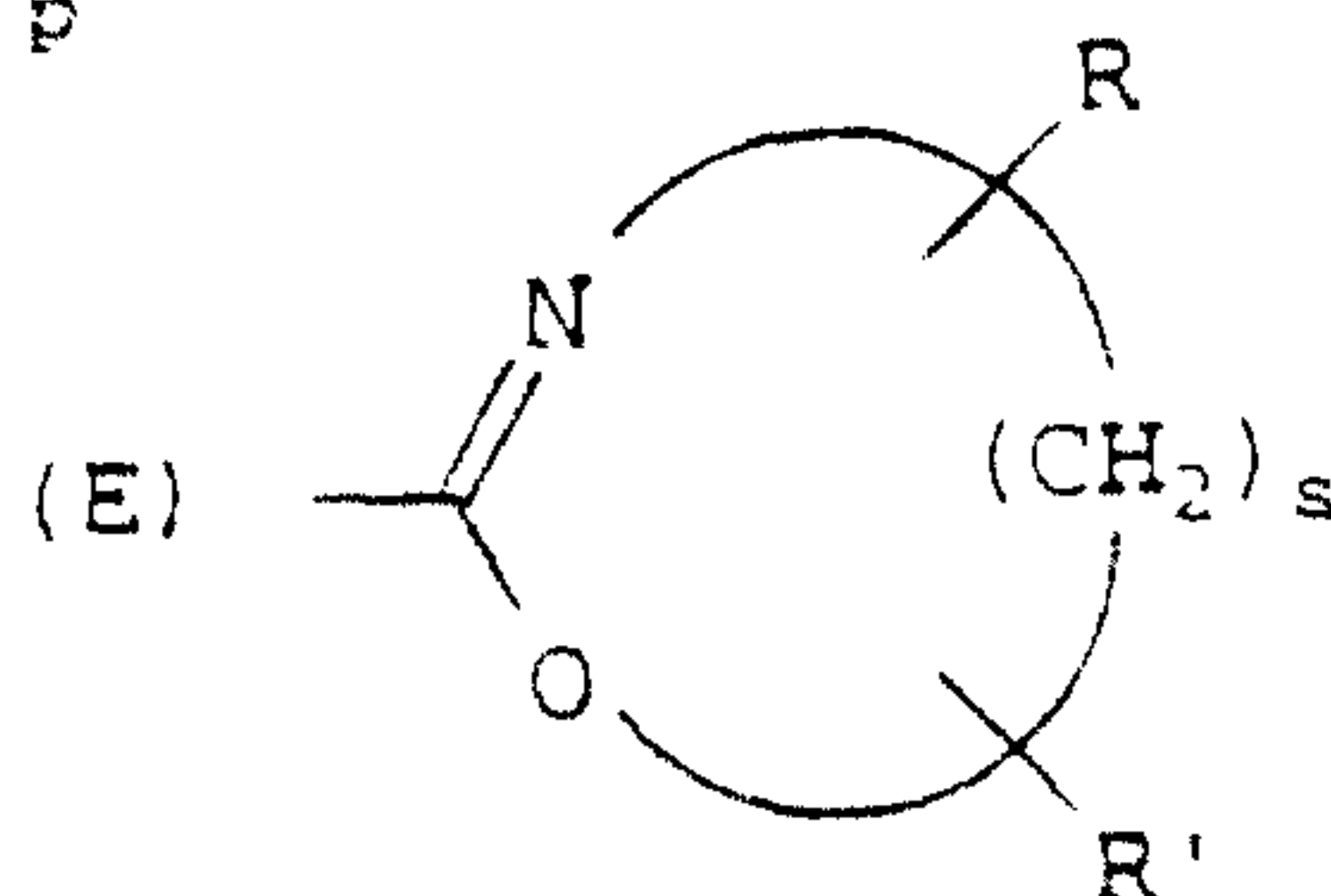
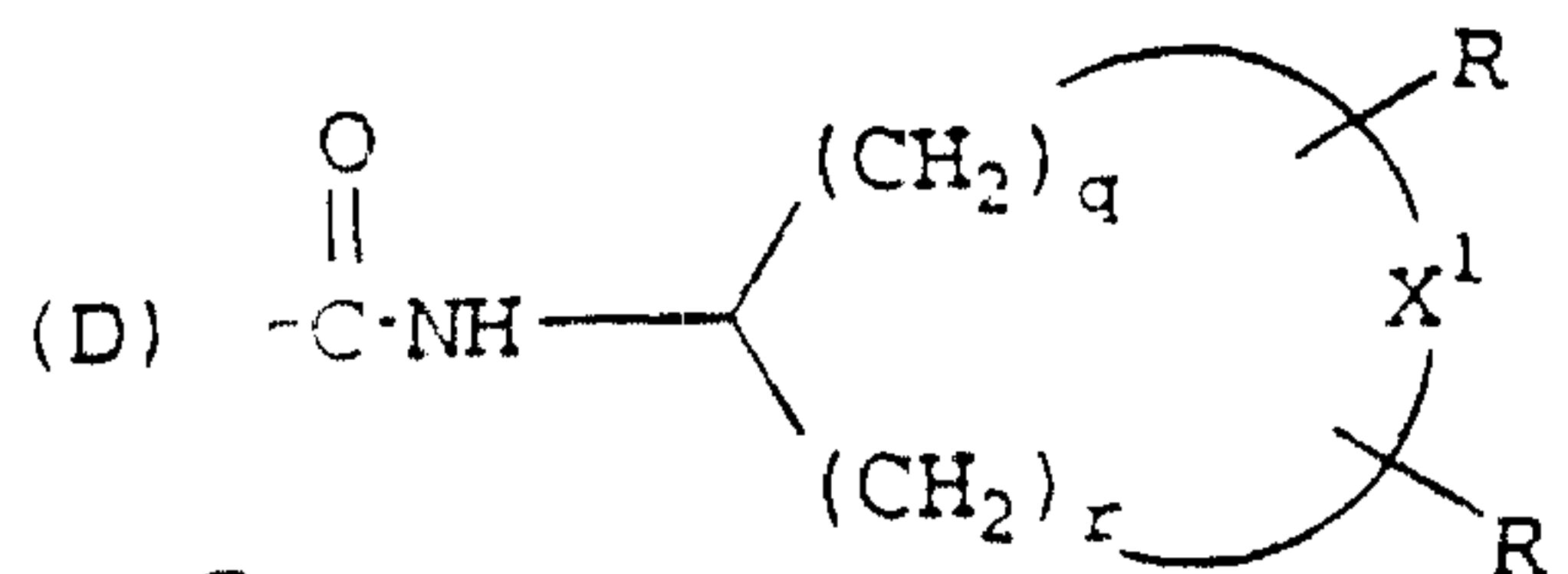
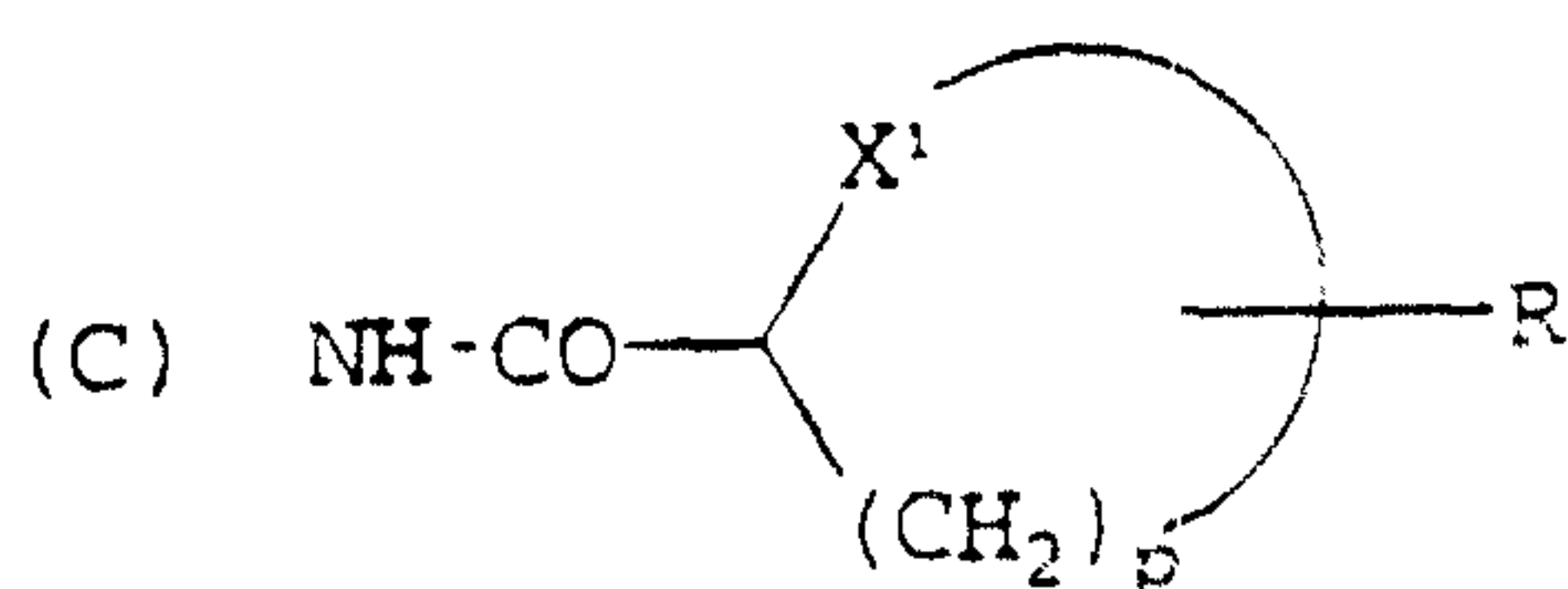
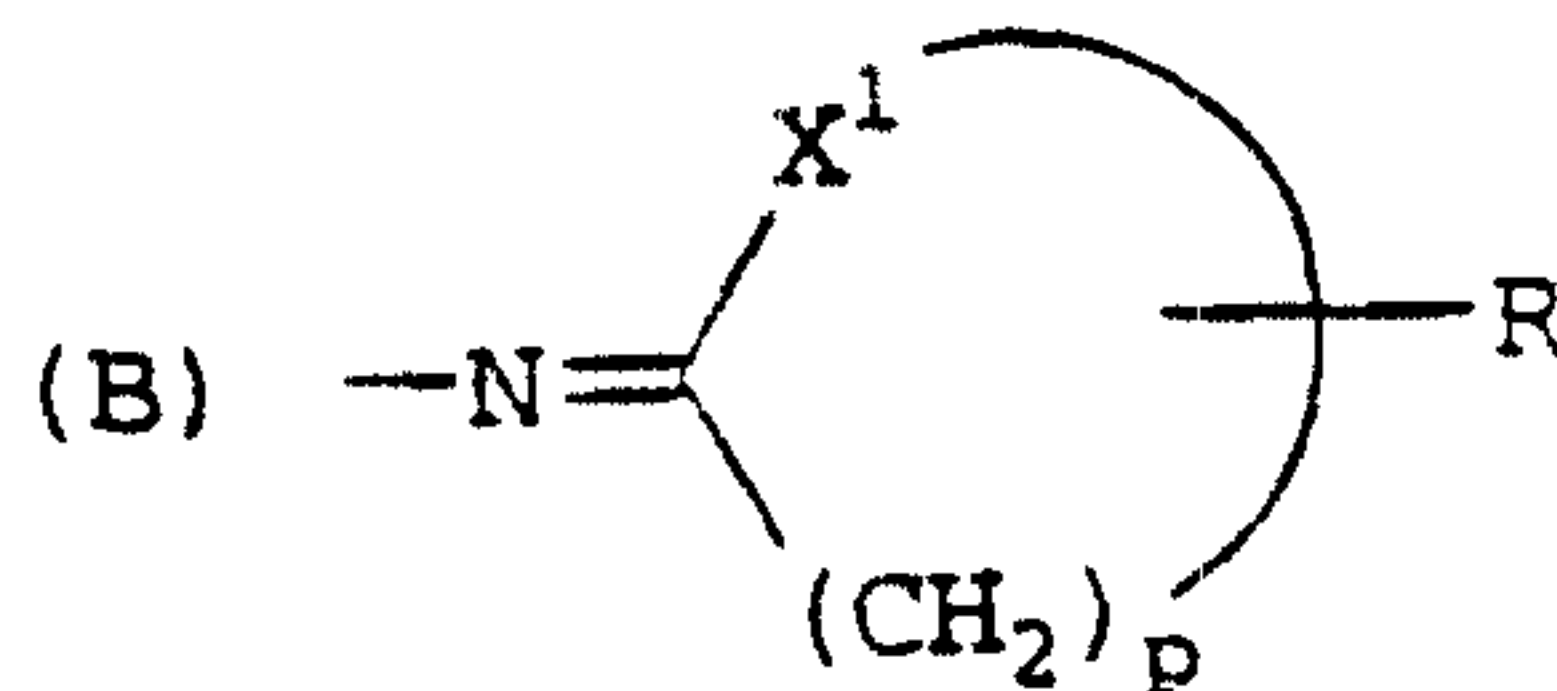
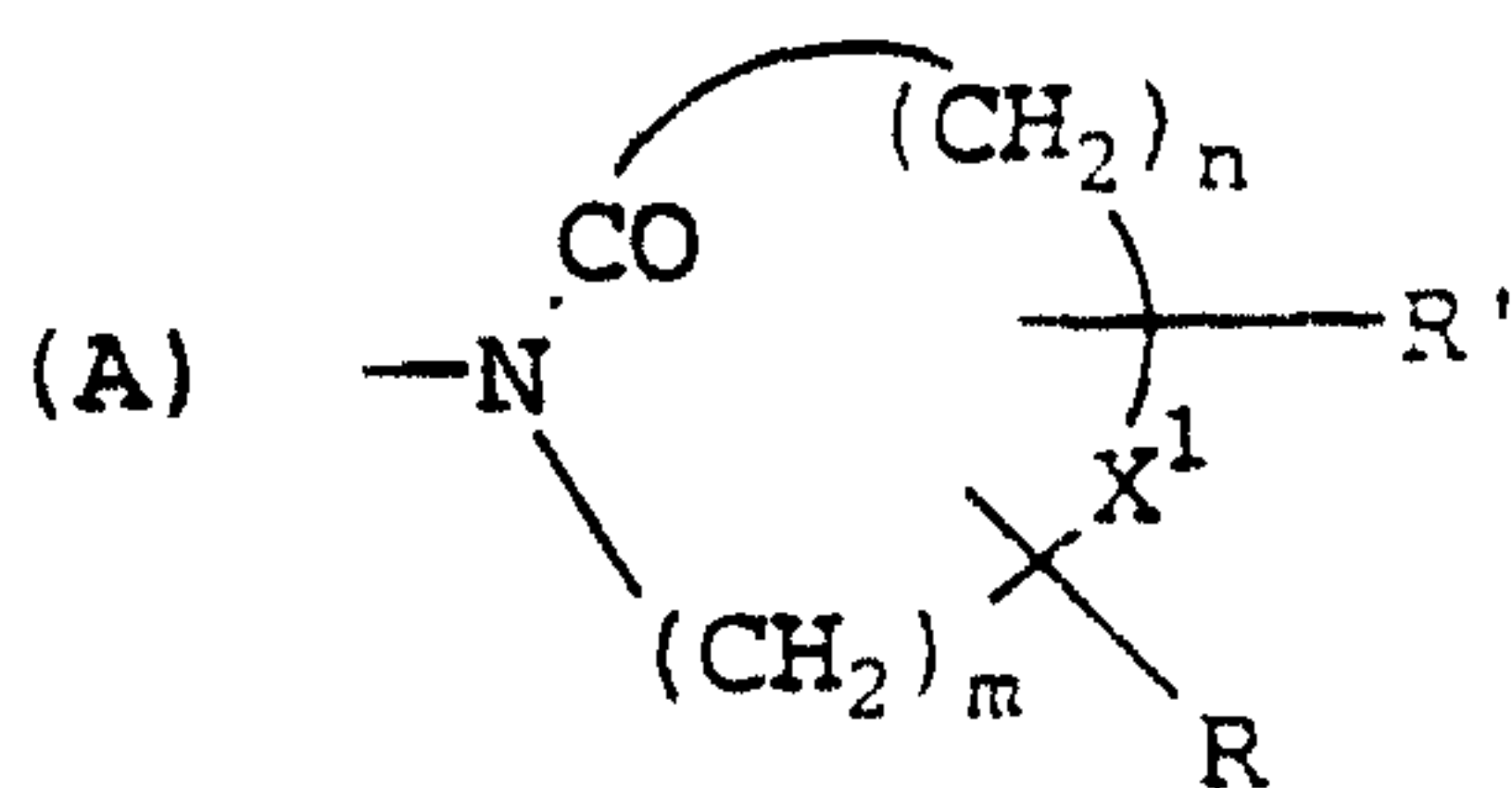
What is claimed is:

1. Use of an image enhancing amount of a radiocontrast triiodinated phenyl compound of formula (I) substituted with one or more heterocyclic groups for reducing the risk of clot formation in a diagnostic procedure in a patient subjected to said diagnostic procedure, wherein formula (I) is

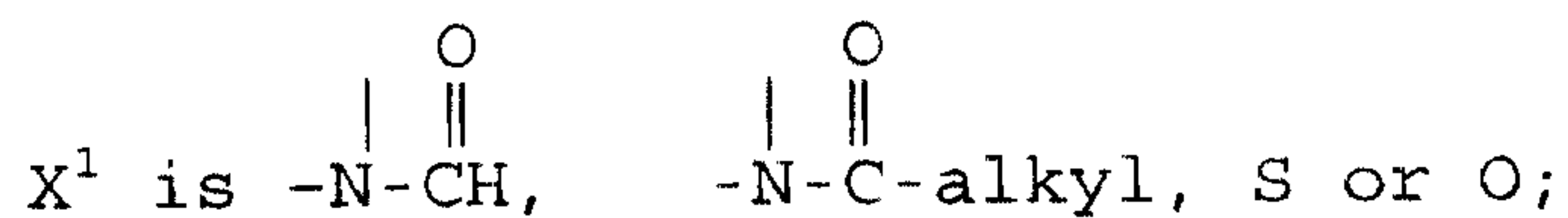


(I)

in which R_1 is $-\text{CO}-\text{NR}_4\text{R}_6$, R_3 is a heterocyclic group selected from



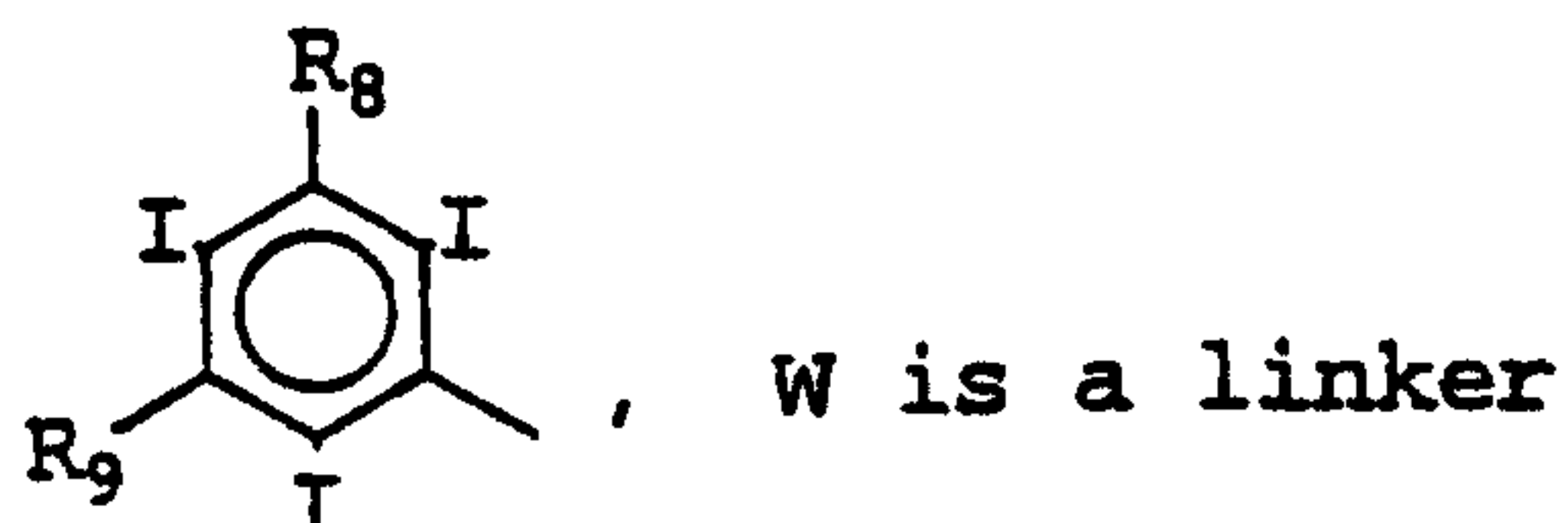
wherein R and R' are independently selected from $-\text{OH}$, C_{1-6} alkyl, alkoxy, hydroxyalkyl, alkoxyalkyl, and $-\text{H}$, but not both R and R' being $-\text{H}$ simultaneously;



- 45 -

m is 1-4; n is 0-3; p is 2-5; q and r are independently 1 or 2; and s is 2-5;

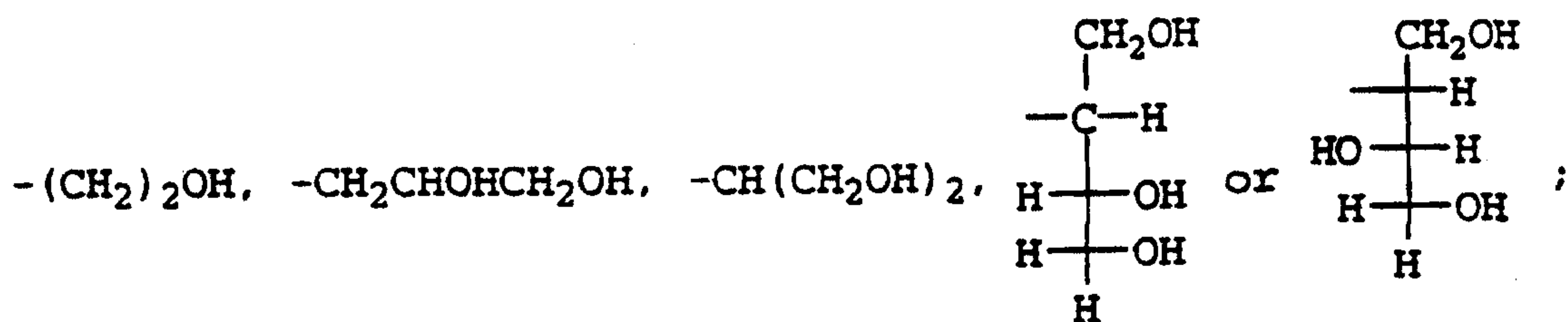
R₂ is -CO-NR₅R₇, or a group -WZ where Z is



R₈ is -CO-NR₁₀R₁₂, R₉ is -CO-NR₁₁R₁₃ or a heterocyclic group as defined above for R₃;

R₄, R₅, R₁₀ and R₁₁ are the same or different and are -H, -CH₃ or -(CH₂)₂OH;

R₆, R₇, R₁₂ and R₁₃, are the same or different and are -H,



W is -X-Y-X-, wherein X is -NR₁₄-CO- or -CO-NR₁₄-;

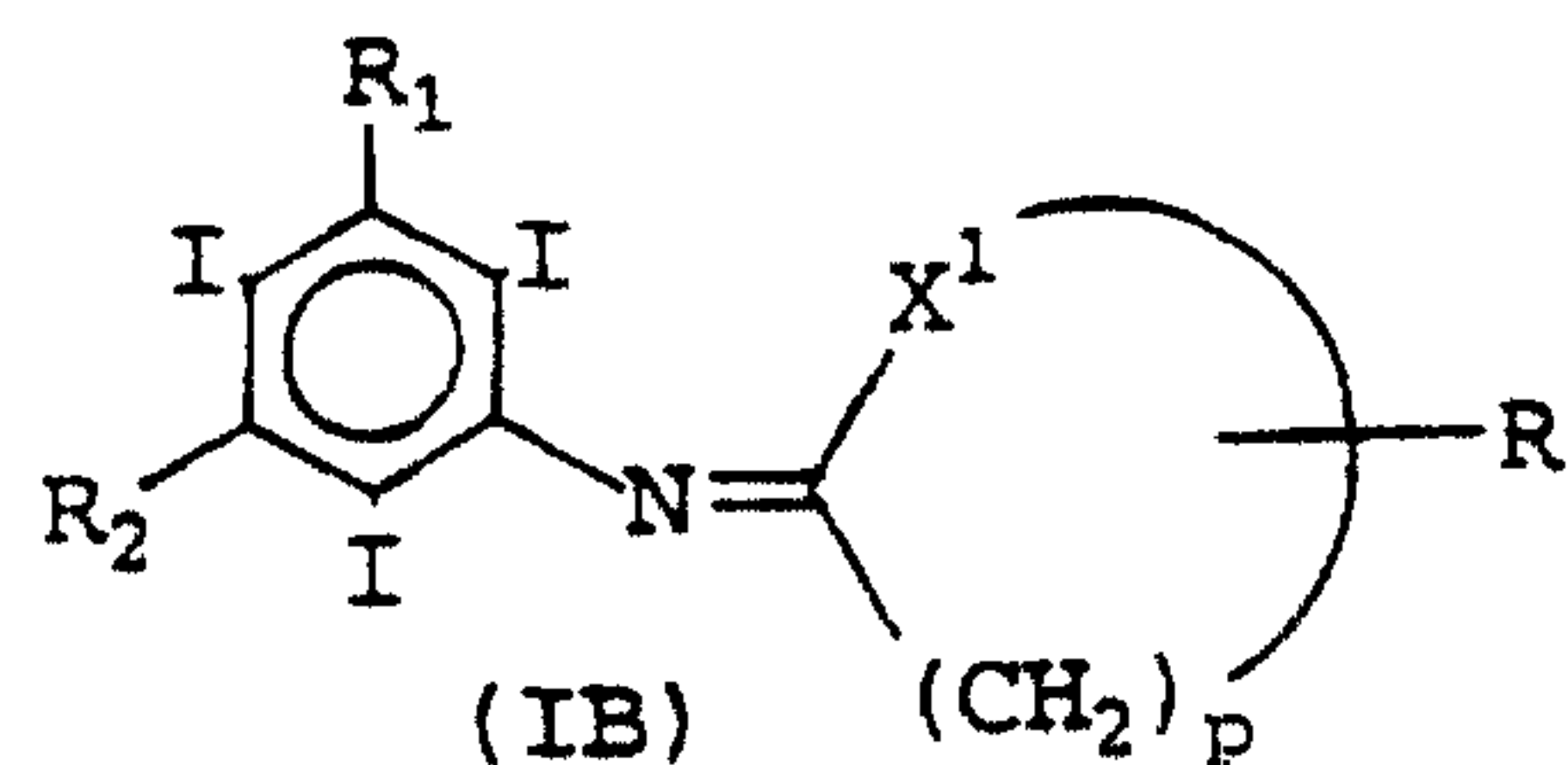
Y is -CH(R₁₄)-A-[CH(R₁₄)]_n-; R₁₄ and R₁₄' are -H, -alkyl, or -hydroxyalkyl; A is a single bond, -O-, -S-, or -NR₁₄CO-; and n is 0 to 6.

2. The use according to claim 1, wherein said heterocyclic group is substituted with 0 to 2 -OH groups, and R₁ and R₂ carry a total of 3 to 4 -OH groups.

3. The use according to claim 1, wherein the compounds are selected from the 3HM5-iomophol-A, 2HM5-iopryol-A, 5HM-iofurol-A, 3H2-iopyrol-A, 3H2-iopyrol-S, 3H2-iopiperidol-A, 2-iopyrol-A, 2-iopiperidol-A.

4. A compound of formula

- 46 -



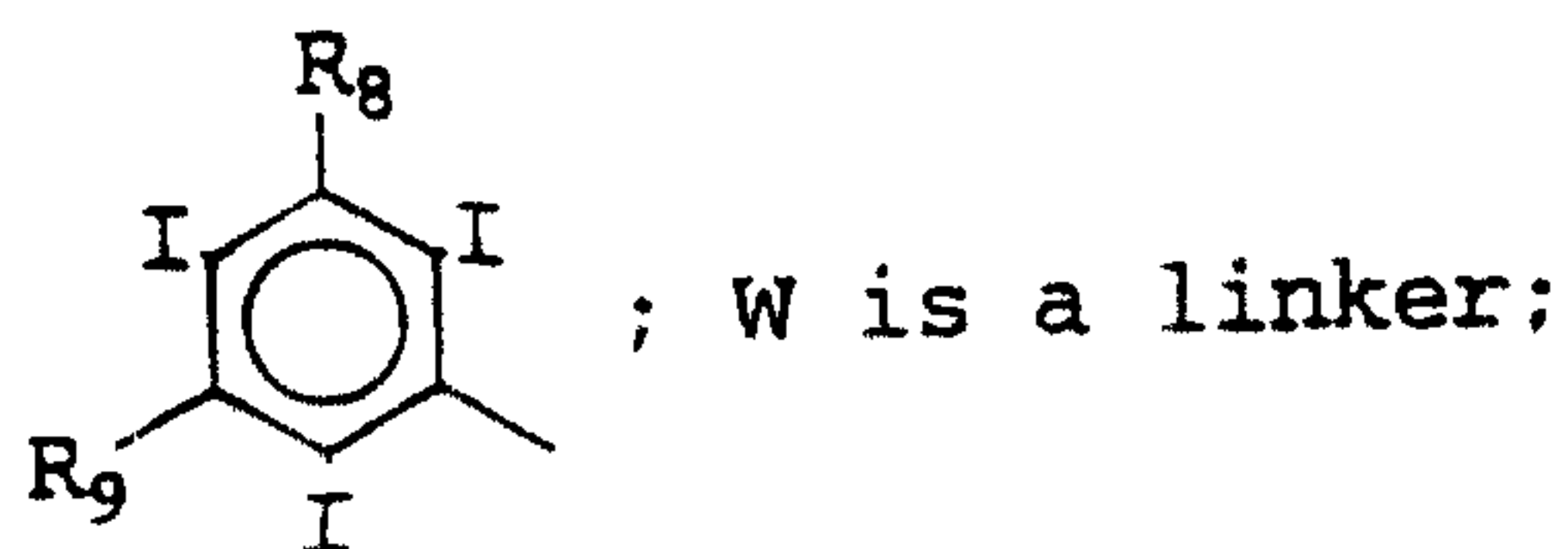
wherein R is selected from -H, -OH, C₁₋₆ -alkyl, -alkoxy, -hydroxyalkyl and -alkoxyalkyl;

X¹ is -N(CHO)-, -N(CO-alkyl)-, -S-, or -O-;

p is 2-5;

R₁ is -CO-NR₄R₆; R₂ is -CO-NR₅R₇;

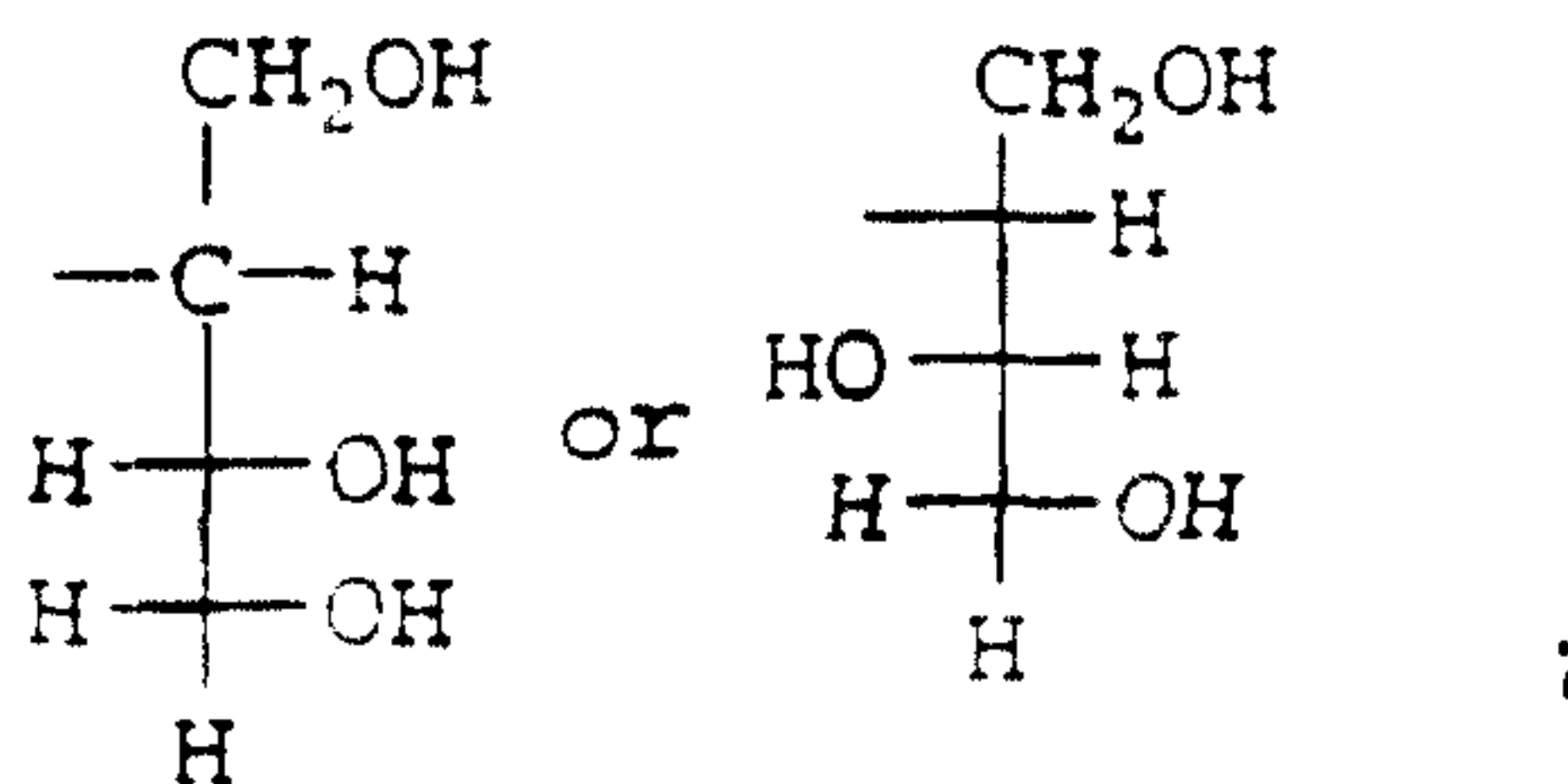
or R₂ can be -W-Z, where Z is



R₈ is -CONR₁₀R₁₂, or heterocyclo; R₉ is -CO-NR₁₁R₁₃, or heterocyclo;

R₄, R₅, R₁₀ and R₁₁ are the same or different and are -H, -CH₃ or -(CH₂)₂OH;

R₆, R₇, R₁₂, and R₁₃ are the same or different and are -H, (CH₂)₂OH, -CH₂-CHOH-CH₂OH, -CH(CH₂OH)₂,



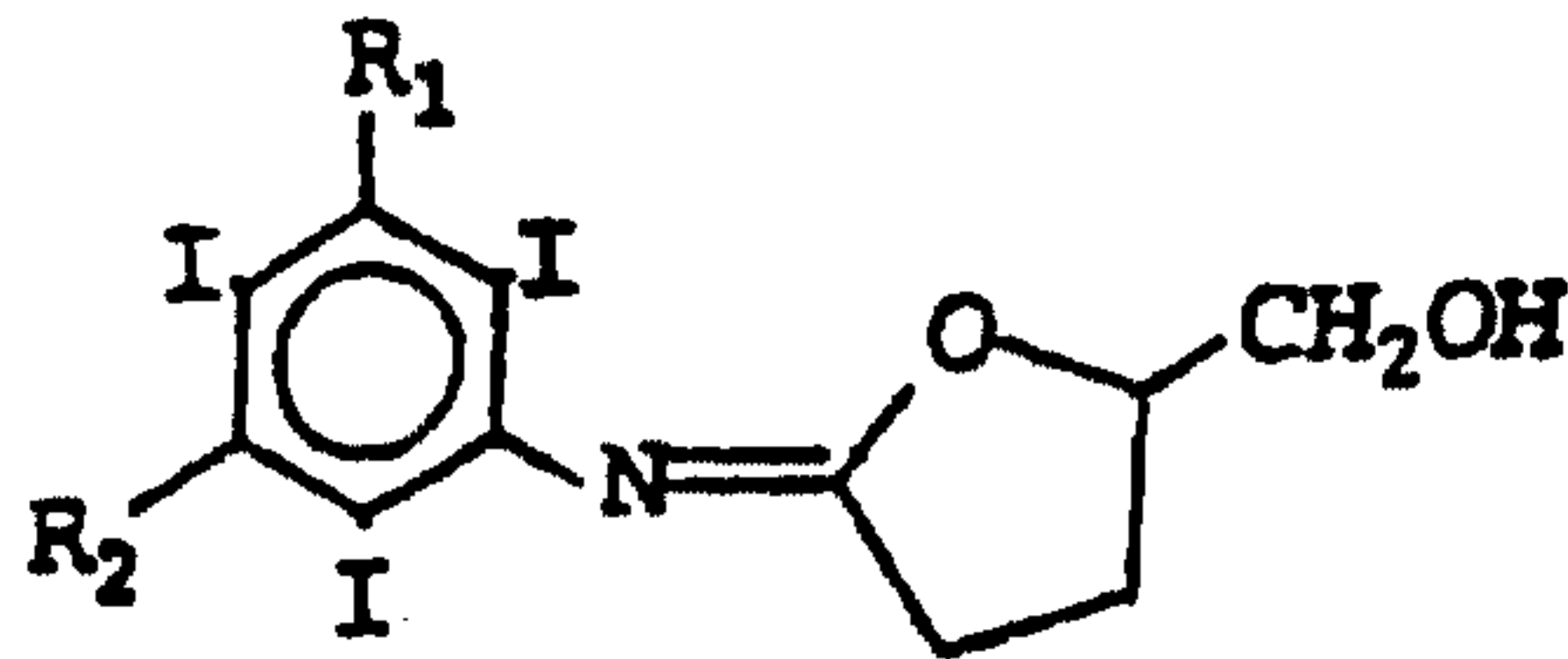
W is -X-Y-X, wherein X is -NR₁₄-CO- or -CO-NR₁₄-;

Y is -CH(R₁₄)-A-[CH(R₁₄')]_n-; R₁₄ and R₁₄' are -H, -alkyl, or -hydroxyalkyl; A is a single bond, -O-, -S-, or -NR₁₄CO-; and n is 0 to 6.

5. The compound of claim 4, wherein X¹ is oxygen, p is 3, R is hydroxyalkyl, R₄ and R₅ are each -H, and R₆ and R₇ are each hydroxyalkyl.

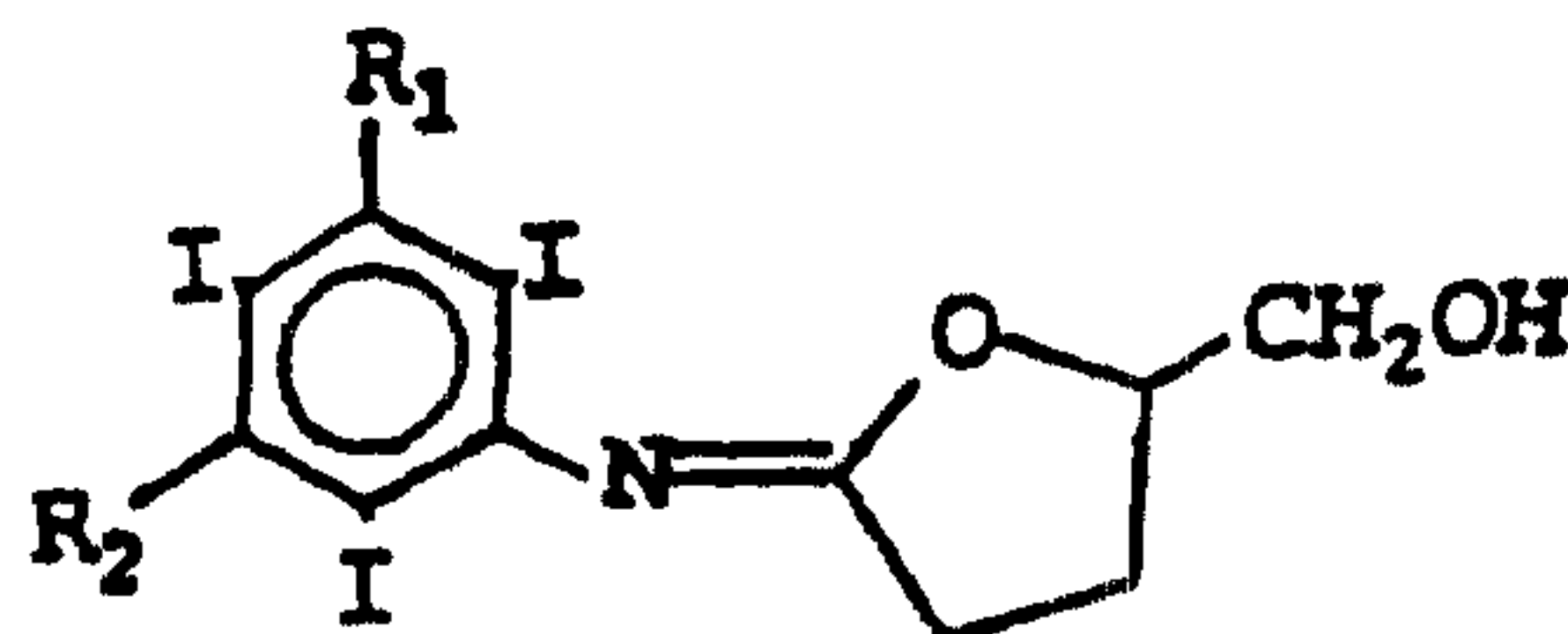
- 47 -

6. A compound of claim 4 of formula



wherein R_4 and R_5 are each H; and R_6 and R_7 are each $-\text{CH}_2-\text{CHOHCH}_2\text{OH}$.

7. A compound of claim 4 of formula



wherein R_4 and R_5 are each H; R_6 and R_7 are each $-\text{CH}(\text{CH}_2\text{OH})_2$.

8. A compound of claim 6, having the name [N,N'-bis(2,3-dihydroxypropyl)]-5-[[dihydro-5-(hydroxymethyl)-2(3H)-furanylidene]amino]-2,4,6-triiodo-1,3-benzenedicarboxamide.

9. A compound of claim 6, having the name 5-[[dihydro-5-(hydroxymethyl)-2(3H)-furanylidene]amino]-N,N'-bis[(2-hydroxy)-1-(hydroxymethyl)ethyl]-2,4,6-triiodo-1,3-benzenedicarboxamide.

10. A pharmaceutical composition comprising a compound as defined in claim 4 and a pharmaceutically acceptable carrier.

11. A use of an image enhancing amount of the composition of claim 10 for reducing the risk of clot formation in a diagnostic procedure in a patient subjected to said diagnostic procedure.