

PATENT SPECIFICATION

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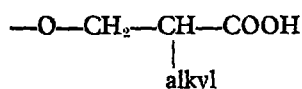
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(54) TRIIODO-PHENYLALKYL ETHERS, THEIR APPLICATION
 IN X-RAY CONTRAST AGENTS AND PROCESS FOR THEIR
 PRODUCTION

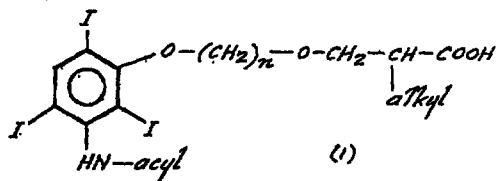
(71) We, BRACCO INDUSTRIA
 CHIMICA SOCIETA PER AZIONI, 50,
 Via E.Folli, Milan, Italy, an Italian body
 corporate, do hereby declare the invention, for
 which we pray that a patent may be granted
 to us, and the method by which it is to be per-
 formed, to be particularly described in and by
 the following statement:—

- The present invention is concerned with tri-
 iodophenyl-alkyl ethers which are novel by
 virtue of containing the 3-oxy-2-alkyl-
 propionic acid radical of the formula



- and with X-ray contrast agents which contain
 these new ethers as shadow-giving compon-
 ents.

- In particular, the present invention provides
 3 - [(3 - acylamino - 2,4,6 - triiodo - phen-
 oxy) - alkoxy] - 2 - alkyl - propionic acids of
 the general formula



in which acyl represents an acetyl or propionyl
 group; n is 2, 3 or 4; and alkyl represents a
 methyl or ethyl radical;

- their physiologically acceptable metal and
 amine salts; and compositions of X-ray con-
 trast agents containing at least one of these
 as a shadow-giving component and a carrier.

- The preferred shadow-giving components
 are 3 - [2 - (3 - acetyl-amino - 2,4,6 - triiodo -

phenoxy) - ethoxy] - 2 - ethyl - propionic
 acid and its physiologically acceptable alkali
 metal, calcium, magnesium or alkanolamine
 salts.

These X-ray contrast agents are especially
 well suited for application in cholezysto-
 graphy. They are preferably administered *per*
os.

Compared with the best gall contrast agents
 for oral administration which are used today,
 i.e.

IODOPANOIC ACID

[3 - (3 - amino - 2,4,6 - triiodo - phenyl) -
 2 - ethyl propionic acid];

IOPODATE

[3 - (3 - dimethylamino - methylene - amino -
 2,4,6 - triiodo - phenyl) - propionic acid];

and the known compound with the most close-
 ly related structure, 2 - [2 - (3 - N - ethyl -
 acetyl-amino - 2,4,6 - triiodo - phenoxy) -
 ethoxy] - propionic acid (IODOXANIC
 ACID: Swiss Patent Specification No.
 483,262), the new shadow-giving components
 have the following advantages:

—the bilitropism of the new compounds is
 substantially higher and the biliary trans-
 port maxima [G. Müller *et al*, Schweiz. med.
 Wochenschrift 99, 577—581 (1968)] are
 higher. Accordingly, the contrast pictures
 of the gall organs are substantially im-
 proved;

—the gall ducts are regularly visible for the
 first time;

—the compatibility is considerably higher,
 especially the intravenous compatibility
 which is a substantially more objective
 measure for the innocuousness of a com-
 pound than is the oral toxicity which strong-
 ly depends on the method of application
 and the individual absorption;

- the excretion is much faster; no intestinal residues are observed;
- the nephrotoxicity is substantially lower than, for example, that of IODOPANOIC ACID which is still the compound most commonly used today;
- due to the omission of the N-alkyl group contained in the compounds of Swiss Patent Specification No. 483,262, the geometrical isomerism observed in these compounds does not occur. There is no separation of isomers; the preparation of pure compounds is much simpler and better ensured.
- G. Miller *et al* [*loc.cit*] have shown that for the evaluation of gall contrast agents the biliary transport maximum (T_m), i.e. the transport capacity of the organism, is a decisive value for the contrast agent concerned and that an increase of the dosage beyond this capacity is pointless because it does not lead to an increased excretion of gall or to an improvement of the shadow density. The higher the transport maximum, the higher are the shadow densities and the better are the X-ray contrast pictures which can be achieved.
- The decisive pharmacological properties of the new shadow-giving components A, B, C, D and E, those of the structurally most closely related compound F [IODOXANIC ACID] mentioned above, and those of the two oral gall contrast agents most widely used, G and H, are assembled in the following Table. In all cases, the data were determined by identical methods and under the same external conditions. They are therefore quantitatively comparable.
- The symbols mean:
- A: 3 - [2 - (3 - acetylamino - 2,4,6 - triiodo - phenoxy) - ethoxy] - 2 - ethyl - propionic acid; Example 1.
- B: 3 - [2 - (3 - acetylamino - 2,4,6 - triiodo - phenoxy) - ethoxy] - 2 - methyl - propionic acid; Example 2.
- C: 3 - [3 - (3 - acetylamino - 2,4,6 - triiodo - phenoxy) - propoxy] - 2 - ethyl - propionic acid; Example 3.
- D: 3 - [4 - (3 - acetylamino - 2,4,6 - triiodo - phenoxy) - butoxy] - 2 - ethyl - propionic acid; Example 4.
- E: 3 - [2 - (3 - propionylamino - 2,4,6 - triiodo - phenoxy) - ethoxy] - 2 - ethyl - propionic acid; Example 7.
- F: 2 - [2 - (3 - N - ethyl - acetylamino - 2,4,6 - triiodo - phenoxy) - ethoxy] - propionic acid [IODOXANIC ACID] (Swiss Patent Specification No. 483,262)
- G: 3 - (3 - amino - 2,4,6 - triiodo - phenyl) - 2 - ethyl - propionic acid [IODO-PANOIC ACID]
- H: 3 - (3 - dimethylaminomethylene - amino - 2,4,6 - triiodo - phenyl) - propionic acid [IOPODATE]
- Cholezystography**
(Indices according to Hoppe):
Evaluation of shadow density and quality of contrast picture:
- 0=negative
1=weak
2=sufficient
3=good
4=excellent
- [J. O. Hoppe, J. Amer. Pharm Assoc. Sci. Ed. 48, pp 368—379 (1959)]
- Gall ducts:**
Evaluation: — =negative or only occasionally visible
+ =regularly visible
++ =optimum visibility

Pharmacology: Quantitative comparative data

Compound	Toxicity DL 50/ mg/kg in mice (M) and rats (R)		Cholecystography: indices acc. to Hoppe in dogs (1), cats (2) after administration of (a) 100 and (b) 200 mg test substs./kg body weight per os, after:								Gall ducts	Biliary transport maximum)1 in dogs (= transport capacity) micromol.kg ⁻¹ .min ⁻¹
	per os	i.v.										
			2 h.	4 h.	6 h.	8 h.	24 h.	32 h.				
A	M: 2620	1090	(1/a)	1	2	2.5	2.5	3	2.5	++ ++ ++	0.94 — 0.95	
	R: 3800	1000	(1/b)	2.5	3	3.5	4	4	4			
			(2/b)	3	3	3	3.5	4	3.5			
B	M: 5200	1150	(1/a)	0.5	2.5	2.5	2.5	2	2			
			(1/b)	2	2	3	3	3	3			
C	M: 3700	750	(1/b)	2	2.5	2.5	2.5	2.5	2.5			
D	M: 2200	610	(1/b)	2	2.5	3	3	3	3			
E	M: 2800	860	(1/b)	2	2.5	3	2.5					
F	M: 1600	425	(1/a)	0	1	2.25	2.75	2	2	—	0.69 — 0.77	
	R: 2860	445	(1/b)	2	2.75	3	3.25	2.75	2.75			
G	M: 1540	285	(1/a)	0.5	1	1.75	2.25	2.75	2.75	—	0.22 — 0.23	
	R: 2870	320	(1/b)	1.25	2.5	2.75	2.25	0.5	0.5			
H	M: 855	240	(1/b)	1	1.5	1.5	2	0.5	0.5	— + (+))2	0.68 — 0.74)3	
	R: 2500	303										

)1 Technique: Rosati *et al*, Investigative Radiology, Vol. 5, No. 4, 232 (1970).

)2 Special technique required: Diss. W. Segerer, Munich 1968.

)3 Maximum not yet completely reached, but higher dosage leads to death of part of the animals.

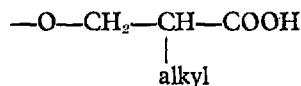
Results:

The considerable advance of the shadow-giving compounds A—E obtained according to the invention, particularly of the compound A, over the state of the art (compounds F, G and H) in respect of compatibility, biliary transport capacity, quality of cholezystography and portrayal of the gall ducts is obvious.

The most important advance for the physician consists in the regular portrayal of the gall ducts. In general, this has hitherto only been possible with the aid of intravenously applicable gall contrast agents, and their application is restricted to hospitals for reasons of safety, since time and again grave incidents occur.

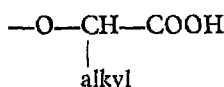
Another essential advantage for the practitioner consists in the improved compatibility which permits of a higher and more effective dosage. Due to the rapid excretion and the absence of intestinal residues which otherwise occur with higher dosage, the present new compounds permit of an efficient utilisation of the higher dosage. The contrast pictures are not impaired by interfering shadows from the intestinal region.

These advances over the state of the art are predominantly due to the 3 - oxy - 2 - alkyl - propionic acid group of the formula



which is new in this class of compounds.

The known structurally comparable compounds always contain the classical 2 - oxy - 2 - alkyl - acetic acid group of the formula



and their bilitropic properties are substantially less marked.

Even the 2 - oxy - 2 - alkyl - acetic acid derivatives of the Swiss Patent Specification No. 483,262 mentioned above, such as e.g. IODOXANIC ACID, which contain an additional N-alkyl group, exhibit substantially weaker bilitropic properties, although N-alkylation is normally attended with a strengthening of the bilitropism, though also with an increase in toxicity (see Table I on page 2 of the aforesaid Swiss Patent Specification).

With the aid of the present invention it was possible for the first time to obtain gall contrast agents for oral application of sufficient effectiveness, which contain the acylamino group non-alkylated on the nitrogen atom, which imparts very good tolerance.

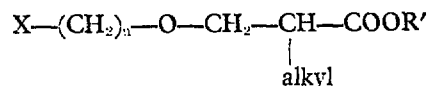
The new compounds can be used as free acids or in the form of their physiologically well tolerated metal and amine salts.

Suitable metal salts are the sodium, lithium, calcium and/or magnesium salts.

As amine salts, there are preferably used salts of alkanolamines, for example, of N - methyl - glucamine, N - methyl - xylamine (= 1 - methylamino - 1 - desoxy - [D] - xylite), 1 - methylamino - 2,3 - propane - diol, diethanolamine, and others.

Mixtures of these salts can also be used.

The present invention also relates to the preparation of the new shadow-giving 3 - [(3 - acylamino - 2,4,6 - triiodo - phenoxy) - alkoxy] - 2 - alkyl - propionic acids of the general formula (I), which is characterised in that a 3 - acylamino - 2,4,6 - triiodo - phenol is etherified by the reaction with a reactive 3 - alkoxy - 2 - alkyl - propionic acid derivative of the general formula



in which X means the reactive radical of a strong acid, i.e. a halogen radical, chlorine, bromine or iodine, or a sulphate or sulphonate radical; *n* means an integer 2, 3 or 4; alkyl means a methyl or ethyl group; and —COOR' means a carboxylic acid ester or carboxylate group; when the group —COOR' is an ester the product being hydrolyzed;

and the corresponding 3 - [(3 - acylamino - 2,4,6 - triiodo - phenoxy) - alkoxy] - 2 - alkyl - propionic acid is subsequently isolated. It is preferred to carry out this process when, in the above compounds, "acyl" is acetyl, "alkyl" is ethyl and an alkyl ester is formed and then hydrolyzed.

Etherification is carried out either in the presence of a basic condensation agent consisting of an alkali metal alcoholate or alkali metal carbonate, or with the use of a corresponding alkali metal 3-acylamino - 2,4,6 - triiodo phenolate.

The reactive 3 - alkoxy - 2 - alkyl - propionic acid derivative used for etherification is usually a 3 - (halo - alkoxy) - 2 - alkyl - propionic acid ester, and the resultant 3 - [(3 - acylamino - 2,4,6 - triiodo - phenoxy) - alkoxy] - 2 - alkyl - propionic acid ester is subsequently hydrolysed.

EXAMPLES OF PROCESSES AND COMPOUNDS**Example 1**

3 - [2 - (3 - acetyl-amino - 2,4,6 - triiodo - phenoxy) - ethoxy] - 2 - ethyl - propionic acid

(a) *Ethyl ester*

A solution of 192 g sodium 3 - acetyl-amino - 2,4,6 - triiodo phenolate (0.35 mol) in 350 ml dimethyl-acetamide is mixed with stirring at

- 90°C within 20—30 minutes with 107.5 g 3 - (2 - iodoethoxy) - 2 - ethyl - propionic acid ethyl ester (0.35 mol). The mixture is stirred at 95—100°C for 16 hours, the solvent is then distilled off in a vacuum, and the residue is poured in 4000 ml of water. The precipitated solid product is thoroughly washed with water, a dilute sodium carbonate solution, a dilute sodium hydrogen sulphite solution, and finally again with water. Yield: 220 g (90% of theory). Melting point (after recrystallisation from 75% aqueous ethanol: 85—86°C.
- $C_{17}H_{22}I_3NO_5$ calc. C 29.12% I 54.31%
found C 29.15% I 54.53%.
- Thin layer chromatograph (T.C.) on silica gel with chloroform/glacial acetic acid = 19:1. R_f = 0.57.
- (b) *Free acid*
- 100 ml of a 1N sodium hydroxide solution are added in portions with stirring to 70 g of the ethyl ester (0.1 mol) in a boiling mixture of 250 ml methanol and 250 ml of water. The methanol is distilled off, the residue is mixed with water and extracted with ethyl acetate; the aqueous phase is acidified with hydrochloric acid in the presence of sodium hydrogen sulphite.
- The free acid gradually crystallises. It melts after recrystallisation from 50% ethanol and from ethyl acetate at 130°C.
- $C_{15}H_{18}I_3NO_5$ calc. C 26.77% I 56.57%
found C 26.69% I 56.75%.
- T.C. on silica gel with chloroform/glacial acetic acid = 19:1. R_f = 0.32.
- Solubility: insoluble in water, soluble in chloroform, readily soluble in methanol and ethanol; sodium salt: 50 g/100 ml water at 20°C; N-methyl-glucamine salt (MGA salt): 100 g/100 ml water at 20°C.
- The 3 - (2 - iodoethoxy) - 2 - ethyl - propionic acid ethyl ester used as starting material is prepared as follows:
- (1) 0.8 mol ethyl-malonic acid diethyl ester are reacted in ethyl ether with 0.84 mol sodium hydride and then with 0.8 mol (2 - chloroethoxy) - methyl chloride. The resultant 2 - (2 - chloroethoxy - methyl) - 2 - ethyl - malonic acid diethyl ester is isolated; b.p. 136—144°C/4 mm Hg.
- (2) 0.47 mol 2 - (2 - chloroethoxy - methyl) - 2 - ethyl - malonic acid diethyl ester are partially hydrolysed in 500 ml of 60% aqueous methanol with 0.5 mol sodium hydroxide by heating at 60—65°C for 2 hours. The 2 - (2 - chloroethoxy - methyl) - 2 - ethyl - malonic acid monoethyl ester obtained by acidification and extraction with ethyl ether after evaporation of the methanol is decarboxylated by heating at 140—150°C.
- The 3 - (2 - chloroethoxy) - 2 - ethyl - propionic acid ethyl ester thus formed is isolated.
B.p. 119—124°C/14 mm Hg.
- (3) 0.325 mol 3 - (2 - chloroethoxy) - 2 - ethyl - propionic acid ethyl ester are reacted with 0.65 mol sodium iodide in 300 ml ethanol by boiling under reflux for 16 hours. The resultant 3 - (2 - iodoethoxy) - 2 - ethyl - propionic acid ethyl ester is isolated; b.p. 125—128°C/3—4 mm Hg; n_D^{20} : 1.482.
- Example 2**
- 3 - [2 - (3 - acetylamino - 2,4,6 - triiodo - phenoxy) - ethoxy] - 2 - methyl - propionic acid
- (a) *Ethyl ester*
- A solution of 165 g of the sodium salt of 3 - acetyl - amino - 2,4,6 - triiodo - phenol (0.3 mol) in 350 ml dimethyl acetamide is reacted with 85.5 g 3 - (2 - iodoethoxy) - 2 - methyl - propionic acid ethyl ester (0.3 mol) according to the method described in Example 1(a).
Yield: 192 g (93% of theory).
Melting point (after recrystallisation from ethyl acetate): 125°C.
- $C_{16}H_{20}I_3NO_5$ calc. C 27.97% I 55.42%
found C 27.77% I 55.85%.
- T.C. on silica gel with chloroform/glacial acetic acid = 19:1. R_f = 0.54.
- (b) *Free Acid*
- 134.4 g of the ethyl ester (0.2 mol) are hydrolysed in boiling 35% aqueous methanol with 52 ml of a 4N sodium hydroxide solution. The free acid is isolated from the solution of its sodium salt according to the method described in Example 1(b).
Yield: 119 g (90% of theory).
Melting point (after recrystallisation from ethyl acetate): 151°C.
- $C_{14}H_{16}I_3NO_5$ calc. C 25.51% I 57.77%
found C 25.48% I 57.72%.
- T.C. on silica gel with chloroform/glacial acetic acid = 19:1. R_f = 0.34.
- Solubility: insoluble in water, soluble in chloroform, readily soluble in methanol and ethanol; sodium salt: 30 g/100 ml water at 20°C
MGA salt: 60 g/100 ml water at 20°C.
- The 3 - (2 - iodoethoxy) - 2 - methyl - propionic acid ethyl ester used as starting material is prepared in analogy with the 3 - (2 - iodoethoxy) - 2 - ethyl - propionic acid ethyl ester described in Example 1:
- (1) The reaction of 140 g methyl-malonic acid diethyl ester with 20 g sodium hydride and with 103.2 g 2-chloro-ethoxy-methyl chloride yields 118.7 g 2 - (2 - chloroethoxy - methyl) - 2 - methyl - malonic acid diethyl ester).
B.p. 132—139°C/4 mm Hg.

- (2) Partial hydrolysis of 267 g of this substituted malonic acid diethyl ester with 42 g sodium hydroxide and decarboxylation of the resultant substituted malonic acid monoethyl ester yields 103 g 3 - (2 - chloroethoxy) - 2 - methyl - propionic acid ethyl ester of b.p. 102—105°C/14 mm Hg.
- (3) The reaction of 93 g of this chloro derivative with 144 g sodium iodide yields 98 g 3 - (2 - iodoethoxy) - 2 - methyl - propionic acid ethyl ester of b.p. 119°C/3—5 mm Hg.
- Example 3
- 3 - [3 - (3 - acetyl amino - 2,4,6 - triiodo - phenoxy) - propoxy] - 2 - ethyl - propionic acid
- (a) *Ethyl ester*
- 38.5 g sodium 3 - acetyl amino - 2,4,6 - triiodo phenolate [3 - AcNH - 2,4,6 - triiodo - phenyl - O - Na] in 80 ml dimethyl formamide are reacted with 24.1 g 3 - (3 - iodo-propoxy) - 2 - ethyl - propionic acid ethyl ester by stirring at 70°C for 16 hours.
- The crude product is isolated in analogy with Example 1(a) and then dissolved in ethyl acetate; the solution is washed with a sodium carbonate solution, water, a sodium hydrogen sulphite solution and again with water, dried over sodium sulphate and concentrated by evaporation.
- The amorphous residue is recrystallised from 70% ethanol.
- Yield: 37.5 g (75% of theory).
- 35 Melting point: 81—82°C.
 $C_{18}H_{24}I_3NO_5$ calc. C 30.23% I 53.24%
 found C 30.10% I, 53.53%.
- T.C. on silica gel with benzene/chloroform/glacial acetic acid = 7:3:2. R_f = 0.53.
- (b) *Free acid*
- 26.9 g of the ethyl ester are hydrolysed in 150 ml ethanol and 60 ml of water by heating for 3—8 hours in the presence of 41 ml of a 1N sodium hydroxide solution.
- The crude product is isolated in analogy with Example 1(b)—m.p. 77—80°C—and taken up in 50—100 ml of boiling ethyl acetate; there occurs complete dissolution and soon after crystallisation of the stable, higher melting crystal modification; m.p. 135—137°C.
- Yield: 17 g (64% of theory).
- $C_{16}H_{20}I_3NO_5$ calc. C 27.97% I 55.42%
 found C 28.09% I 55.64%.
- 55 T.C. on silica gel with benzene/chloroform/glacial acetic acid = 7:3:2. R_f = 0.46.
- Solubility: sparingly soluble in water, soluble in 2.5 parts methanol, 7 parts ethanol and appr. 10 parts of boiling chloroform; sodium salt: 50 g/100 ml water at 20°C MGA salt: 100 g/100 ml water at 20°C.
- The 3 - (3 - iodo-propoxy) - 2 - ethyl - propionic acid ethyl ester used as starting material is prepared in analogy with the 3 - (2 - iodoethoxy) - 2 - ethyl - propionic acid ethyl ester from ethyl-malonic acid diethyl ester. The following intermediate products were obtained:
- (1) 2 - (3 - chloropropoxy - methyl) - 2 - ethyl - malonic acid diethyl ester; b.p. 142—148°C/2 mm Hg, n_D^{20} : 1.443.
- (2) 3 - (3 - chloropropoxy) - 2 - ethyl - propionic acid ethyl ester; b.p. 103—107°C/2 mm Hg, n_D^{20} : 1.438.
- (3) 3 - (3 - iodo-propoxy) - 2 - ethyl - propionic acid ethyl ester; b.p. 125—127°C/2 mm Hg, n_D^{20} : 1.478.
- Example 4
- 3 - [4 - (3 - acetyl amino - 2,4,6 - triiodo - phenoxy) - butoxy] - 2 - ethyl - propionic acid
- 27.5 g sodium 3 - acetyl amino - 2,4,6 - triiodo phenolate are reacted with 17.3 g 3 - (4 - iodobutoxy) - 2 - ethyl - propionic acid ethyl ester in 60 ml dimethyl formamide in analogy with Example 3(a).
- The resultant amorphous 3 - [4 - (3 - acetyl amino - 2,4,6 - triiodo - phenoxy) - butoxy] - 2 - ethyl - propionic acid ethyl ester is hydrolysed and converted into the free crystalline acid in analogy with Example 3(b). Melting point: ~120°C.
- $C_{17}H_{22}I_3NO_5$ calc. C 29.12% I 54.31%
 found C 29.16% I 53.99%.
- T.C. on silica gel with benzene/chloroform/glacial acetic acid = 7:3:2. R_f = 0.43.
- Solubility: virtually insoluble, even in boiling water; soluble in appr. 40 parts of cold chloroform, 10 parts of hot chloroform, appr. 7 parts of cold ethanol; very readily soluble in methanol and boiling ethanol.
- sodium salt: 30 g/100 ml water at 20°C. MGA salt: 25 g/100 ml water at 20°C.
- The 3 - (4 - iodobutoxy) - 2 - ethyl - propionic acid ethyl ester used as reagent is prepared in analogy with the homologues from ethyl-malonic acid diethyl ester. The following intermediate products were obtained:
- (1) 2 - (4 - chlorobutoxy - methyl) - 2 - ethyl - malonic acid diethyl ester; b.p. 145—155°C/2 mm Hg; n_D^{20} : 1.446.
- (2) 3 - (4 - chlorobutoxy) - 2 - ethyl - propionic acid ethyl ester; b.p. 117—124°C/2 mm Hg; n_D^{20} : 1.438.
- (3) 3 - (4 - iodobutoxy) - 2 - ethyl - propionic acid ethyl ester; b.p. 137—142°C/2 mm Hg; n_D^{20} : 1.475.
- Example 5
- 3 - [2 - (3 - acetyl amino - 2,4,6 - triiodo - phenoxy) - ethoxy] - 2 - ethyl - propionic acid
- 22 g sodium 3 - acetyl amino - 2,4,6 - tri-

iodo phenolate in 40 ml dimethyl formamide are mixed within 10 minutes with 9.2 g 3 - (2 - chloroethoxy) - 2 - ethyl - propionic acid ethyl ester and reacted by stirring at 110°C for 20 hours to form 3 - [2 - (3 - acetyl amino - 2,4,6 - triiodo - phenoxy) - ethoxy] - 2 - ethyl - propionic acid ethyl ester. The latter is isolated and hydrolysed to form the acid, as described in Example 1. Yield: 15.2 g (56.5% of theory).

The etherification can be accelerated by the addition of 5—7 g sodium iodide.

The 3 - (2 - chloroethoxy) - 2 - ethyl - propionic acid ethyl ester can be replaced for the reaction described above with the corresponding methyl ester, propyl ester, isopropyl ester, butyl ester or with another readily accessible alkyl ester.

Example 6

3 - [2 - (3 - acetyl amino - 2,4,6 - triiodo - phenoxy) - ethoxy] - 2 - ethyl - propionic acid

(a) 14.7 g 3 - acetyl amino - 2,4,6 - triiodo - phenol are reacted with 8.6 g 3 - (2 - iodoethoxy) - 2 - ethyl - propionic acid ethyl ester in the presence of 0.037 mol sodium ethylate in 35 ml ethanol by boiling for 40 hours.

(b) 14.7 g 3 - acetyl amino - 2,4,6 - triiodo - phenol and 8.6 g 3 - (2 - iodoethoxy) - 2 - ethyl - propionic acid ethyl ester in 160 ml methyl ethyl ketone are reacted in the presence of 9 g of anhydrous potassium carbonate by boiling on a reflux condenser for 30—40 hours while stirring.

Isolation and hydrolysis of the 3 - [2 - (3 - acetyl amino - 2,4,6 - triiodo - phenoxy) - ethoxy] - 2 - ethyl - propionic acid ethyl ester obtained according to (a) and (b) is carried out as described in Example 1.

Yields: (a) 10.2 g (54.5% of theory)

(b) 9.6 g (51.3% of theory).

The following compounds are prepared in analogy with the preceding Examples:

Example 7

3 - [2 - (3 - propionyl amino - 2,4,6 - triiodo - phenoxy) - ethoxy] - 2 - ethyl - propionic acid

(a) Ethyl ester

16.95 g sodium 3 - propionyl amino - 2,4,6 - triiodo phenolate (0.03 mol) are reacted in 30 ml dimethyl acetamide with 10 g 3 - (2 - iodoethoxy) - 2 - ethyl - propionic acid ethyl ester (0.033 mol) at 90°C in analogy with Example 1(b).

Yield: 15.2 g (71% of theory).

Melting point (after recrystallisation from ethyl acetate): 86°C.

$C_{18}H_{21}I_3NO_5$ calc. C 30.23% I 53.24%
found C 30.38% I 52.94%.

T.C. on silica gel with benzene/chloroform/glacial acetic acid=7:3:2. $R_f=0.65$.

(b) Free acid

Obtained by hydrolysis of the ethyl ester in analogy with Example 1(b).

Melting point (after recrystallisation from ethyl acetate): 114°C.

$C_{18}H_{20}I_3NO_5$ calc. C 27.97% I 55.42%
found C 28.12% I 55.39%.

T.C. on silica gel with benzene/chloroform/glacial acetic acid=7:3:2. $R_f=0.70$.

Solubility: insoluble in water; readily soluble in chloroform, methanol and ethanol;

sodium salt: 10g/100 ml water at 20°C.

MGA salt: 50 g/100 ml water at 20°C.

Example 8

3 - [2 - (3 - propionyl amino - 2,4,6 - triiodo - phenoxy) - ethoxy] - 2 - methyl - propionic acid

(a) Ethyl ester

Melting point (after recrystallisation from ethanol/water 2:1): 79°C.

$C_{17}H_{20}I_3NO_5$ calc. C 29.12% I 54.31%
found C 29.40% I 54.19%.

T.C. on silica gel with benzene/chloroform/glacial acetic acid=7:3:2. $R_f=0.56$.

(b) Free acid

Melting point (after recrystallisation from ethyl acetate): 145°C.

$C_{17}H_{19}I_3NO_5$ calc. C 26.77% I 56.57%
found C 27.00% I 56.19%.

T.C. on silica gel with benzene/chloroform/glacial acetic acid=7:3:2. $R_f=0.68$.

Further Examples:

3 - [3 - (3 - propionyl amino - 2,4,6 - triiodo - phenoxy) - propoxy] - 2 - ethyl - propionic acid

3 - [3 - (3 - acetyl amino - 2,4,6 - triiodo - phenoxy) - propoxy] - 2 - methyl - propionic acid

3 - [3 - (3 - propionyl amino - 2,4,6 - triiodo - phenoxy) - propoxy] - 2 - methyl - propionic acid

3 - [4 - (3 - propionyl amino - 2,4,6 - triiodo - phenoxy) - butoxy] - 2 - ethyl - propionic acid

3 - [4 - (3 - acetyl amino - 2,4,6 - triiodo - phenoxy) - butoxy] - 2 - methyl - propionic acid

3 - [4 - (3 - propionyl amino - 2,4,6 - triiodo - phenoxy) - butoxy] - 2 - methyl - propionic acid

EXAMPLES OF FORMULATION

For application, the new compounds described above can be used together with any suitable carrier, especially as capsules, granules, tablets, dragees, globules, clysmas, suspensions or solutions. Oral preparations are preferred, particularly micronised forms which are more rapidly absorbed and give better

shadow densities without interfering intestinal residues.

The free acids as well as their metal and amine salts can be used.

- 5 The production of some characteristic forms of application are described in the following Examples.

Example 1 Capsules

- 10 300 g of 3 - [2 - (3 - acetyl-amino - 2,4,6 - triiodo - phenoxy) - ethoxy] - 2 - ethyl propionic acid which has been micronised to a particle size smaller than $4\ \mu$ are intimately mixed with 20.4 g of an interface-active substance (tenside) which consists of a condensation product of ethylene oxide and polypropylene glycol, which is solid at room temperature and which prevents the formation of particle aggregates [e.g. Pluronic F68 ("Pluronic" is a Registered Trade Mark)]; the mixture is passed through a stainless sieve with 324 meshes per sq.cm, and 20.4 g of microcrystalline starch are added.

- 25 The mixture is then moistened with distilled water and then granulated by passing the material through a sieve with 56 meshes per sq.cm and drying it in an air current at 40°C . 7.2 g of a lubricant are then added and the granulate is filled into 600 soft gelatin capsules.

Example 2 Tablets

- 35 5 kg 3 - [2 - (3 - acetyl-amino - 2,4,6 - triiodo - phenoxy) - ethoxy] - 2 - ethyl - propionic acid are pasted in a kneading machine with 2 litres of a starch glue containing 100 g of maize starch. If the moist material is sticky, some dry starch is added. The material is then granulated in a granulating machine and dried in a vacuum. The finished granulate is then mixed with 0.5 kg of maize starch and 25 g of magnesium stearate and pressed to form tablets with a content of 500 mg of active ingredient.

Example 3 Tablets

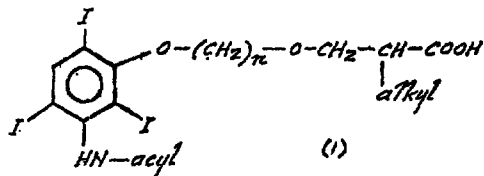
- 45 5 kg of the sodium salt of 3 - [2 - (3 - acetyl-amino - 2,4,6 - triiodo - phenoxy) - ethoxy] - 2 - ethyl - propionic acid and 0.75 kg of granulated sugar (saccharose) are mixed with 0.75 kg of maize starch. The mixture is moistened with 1000 ml of 50% aqueous alcohol and then granulated in a machine. The granulate is dried, sieved, mixed with 0.65 kg of maize starch, 0.05 g of talc and 0.05 kg of magnesium stearate, and pressed to form 10,000 tablets.

Example 4 Dragees

- 60 The granulate obtained according to Example 1 is coated by applying 25% of its weight, of sugar syrup in a coating vessel and subsequently waxed.

WHAT WE CLAIM IS:—

1. 3 - [(3 - Acyl-amino - 2,4,6 - triiodo - phenoxy) - alkoxy] - 2 - alkyl - propionic acids of the general formula



in which acyl represents the acetyl or propionyl group;

n means an integer 2, 3 or 4; and alkyl means a methyl or ethyl radical.

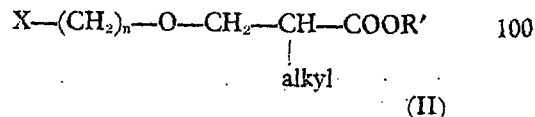
2. Physiologically acceptable metal or amine salts of the compounds claimed in claim 1.

3. 3 - [2 - (3 - Acetyl-amino - 2,4,6 - triiodo - phenoxy) - ethoxy] - 2 - ethyl - propionic acid and its physiologically acceptable alkali metal, calcium, magnesium or alkanolamine salts.

4. A composition of X-ray contrast agent containing a 3 - [(3 - acyl-amino - 2,4,6 - triiodo - phenoxy) - alkoxy] - 2 - alkyl propionic acid of the formula (I) given and defined in claim 1, or a physiologically acceptable metal or amine salt thereof, as shadow-giving component, and a carrier.

5. A composition of X-ray contrast agent according to claim 4, wherein the shadow-giving component is 3 - [2 - (3 - acetyl - amino - 2,4,6 - triiodo - phenoxy) - ethoxy] - 2 - ethyl - propionic acid, or an alkali metal, calcium, magnesium or alkanolamine salt thereof.

6. Process for the production of the compounds claimed in claim 1 or claim 2 which includes etherifying a 3 - acyl-amino - 2,4,6 - triiodo - phenol by reaction with a reactive 3 - alkoxy - 2 - alkyl - propionic acid derivative of the general formula



in which X means the reactive radical of a strong acid, n is 2, 3 or 4; alkyl means a methyl or ethyl group; and $-\text{COOR}'$ means a carboxylic acid ester or a carboxylate group, and when $-\text{COOR}'$ is an ester hydrolyzing the product to obtain a free 3 - [(3 - acyl-amino - 2,4,6 - triiodo - phenoxy) - alkoxy] - 2 - alkyl - propionic acid or salt thereof.

7. Process according to claim 6 wherein X is a chlorine, bromine or iodine radical, or a sulphate or sulphonate radical.

8. Process according to claim 6 or claim 7, including carrying out the etherification either in the presence of a basic condensation agent consisting of an alkali metal alcoholate or alkali



shadow densities without interfering intestinal residues.

The free acids as well as their metal and amine salts can be used.

- 5 The production of some characteristic forms of application are described in the following Examples.

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Example 3 Tablets

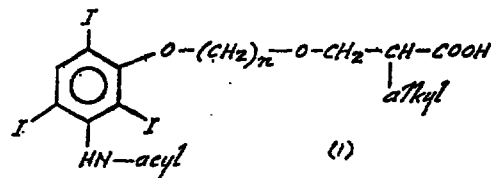
- 45 5 kg of the sodium salt of 3 - [2 - (3 - acetylamino - 2,4,6 - triiodo - phenoxy) - ethoxy] - 2 - ethyl - propionic acid and 0.75 kg of granulated sugar (saccharose) are mixed with 0.75 kg of maize starch. The mixture is moistened with 1000 ml of 50% aqueous alcohol and then granulated in a machine. The granulate is dried, sieved, mixed with 0.65 kg of maize starch, 0.05 g of talc and 0.05 kg of magnesium stearate, and pressed to form 10,000 tablets.

Example 4 Dragees

- 60 The granulate obtained according to Example 1 is coated by applying 25% of its weight, of sugar syrup in a coating vessel and subsequently waxed.

WHAT WE CLAIM IS:—

1. 3 - [(3 - Acylamino - 2,4,6 - triiodo - phenoxy) - alkoxy] - 2 - alkyl - propionic acids of the general formula



in which acyl represents the acetyl or propionyl group;

n means an integer 2, 3 or 4; and alkyl means a methyl or ethyl radical.

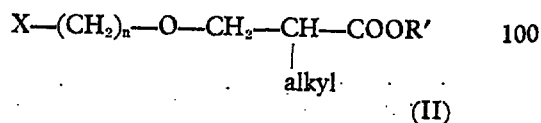
2. Physiologically acceptable metal or amine salts of the compounds claimed in claim 1.

3. 3 - [2 - (3 - Acetylamino - 2,4,6 - triiodo - phenoxy) - ethoxy] - 2 - ethyl - propionic acid and its physiologically acceptable alkali metal, calcium, magnesium or alkanolamine salts.

4. A composition of X-ray contrast agent containing a 3 - [(3 - acylamino - 2,4,6 - triiodo - phenoxy) - alkoxy] - 2 - alkyl propionic acid of the formula (I) given and defined in claim 1, or a physiologically acceptable metal or amine salt thereof, as shadow-giving component, and a carrier.

5. A composition of X-ray contrast agent according to claim 4, wherein the shadow-giving component is 3 - [2 - (3 - acetyl - amino - 2,4,6 - triiodo - phenoxy) - ethoxy] - 2 - ethyl - propionic acid, or an alkali metal, calcium, magnesium or alkanolamine salt thereof.

6. Process for the production of the compounds claimed in claim 1 or claim 2 which includes etherifying a 3 - acylamino - 2,4,6 - triiodo - phenol by reaction with a reactive 3 - alkoxy - 2 - alkyl - propionic acid derivative of the general formula



in which X means the reactive radical of a strong acid, n is 2, 3 or 4; alkyl means a methyl or ethyl group; and $-\text{COOR}'$ means a carboxylic acid ester or a carboxylate group, and when $-\text{COOR}'$ is an ester hydrolyzing the product to obtain a free 3 - [(3 - acylamino - 2,4,6 - triiodo - phenoxy) - alkoxy] - 2 - alkyl - propionic acid or salt thereof.

7. Process according to claim 6 wherein X is a chlorine, bromine or iodine radical, or a sulphate or sulphonate radical.

8. Process according to claim 6 or claim 7, including carrying out the etherification either in the presence of a basic condensation agent consisting of an alkali metal alcoholate or alkali



metal carbonate or with the use of a corresponding alkali metal 3 - acylamino - 2,4,6 - triiodo phenolate.

- 5 9. Process according to claim 6, claim 7 or claim 8, wherein a 3 - (haloalkoxy) - 2 - alkyl - propionic acid ester is used as the reactive 3 - alkoxy - 2 - alkyl - propionic acid derivative for etherification, and the resultant 3 - [(3 - acylamino - 2,4,6 - triiodo - phenoxy) - alkoxy] - 2 - alkyl - propionic acid
- 10 ester is subsequently hydrolysed.

- 15 10. Process according to any one of claims 6 to 9 for the production of 3 - [2 - (3 - acetylamino - 2,4,6 - triiodo - phenoxy) - ethoxy] - 2 - ethyl - propionic acid wherein 3 - acetylamino - 2,4,6 - triiodo - phenol is reacted with a 3 - (2 - haloethoxy) - 2 - ethyl - propionic acid alkyl ester to form the

corresponding 3 - [2 - (3 - acetylamino - 2,4,6 - triiodo - phenoxy) - ethoxy] - 2 - ethyl - propionic acid alkyl ester and the latter is subsequently hydrolysed. 20

11. Processes for the production of the compounds claimed in claim 1 or claim 2 substantially as herein described and exemplified. 25

12. A compound of the formula given and defined in claim 1, or a physiologically acceptable metal or amine salt thereof, whenever produced by a process according to any one of claims 6 to 11. 30

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