Patented Oct. 30, 1951

2,572,828

UNITED STATES PATENT OFFICE

2,572,828

ALKOXYALKYL ESTERS OF MONOIODO-MONO-ALKOXYBENZOIC ACIDS

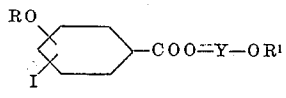
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No Drawing. Application November 24, 1947, Serial No. 787,854

8 Claims. (Cl. 260—473)

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This invention relates to alkoxyalkyl esters of iodoalkoxybenzoic acids, which esters have the formula



where Y is an alkylene bridge and R and R^1 are alkyl groups, and wherein the total number of carbon atoms in the above formula is from 11 to 16. I prefer the compounds wherein Y has 2–3 carbon atoms and R has 1–2 carbon atoms, since these are most readily available from inexpensive starting materials.

Although all possible combinations of the iodo group and the alkoxy group on the benzene ring form useful compounds, certain permutations are preferred because of the relative availability of certain isomers from among the possible alkoxyiodobenzoic acids. The preferred species include alkoxyalkyl esters of 3-iodo-4-alkoxybenzoic acid, 2-iodo-5-alkoxybenzoic acid and 3-iodo-6-alkoxybenzoic acid.

My compounds are opaque to X-rays and therefore are valuable as contrast media in roentgenological examination of body cavities. They may be administered directly into the body cavities to be outlined. They are definite and stable chemical compounds in which the halogen is firmly attached to the benzene nucleus.

I have found that these substances are of particular value in the roentgenological examination of the spinal cord and subarachnoid space, i. e., in that branch of radiography known as myelography. An ideal myelographic agent is one which is easily and rapidly administered and which distributes itself readily and evenly to various parts of the cerebrospinal system, without, however, diffusing into such thin layers that the radiopacity is lost. It should be eliminated readily by adsorption from the spaces rather than requiring aspiration. It should be non-irritating to nerve tissues, and non-toxic in any other way to the patient.

Up to the present time, the various agents used for myelography include gases such as air and oxygen, thorium dioxide sols, iodized oils, and, more recently, a product consisting of a mixture of ethyl esters of isomeric iodophenylundecylic acids. Each of these agents has certain disadvantages. Gases are poor contrast media and are difficult to administer properly, since their use requires removal of part of the cerebrospinal fluid, a procedure which may result in dangerous complications. Thorium dioxide sols have

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been found to cause untoward reactions, as well as introducing the possibility of eventual injury from residual radioactivity. Iodinated and brominated oils such as iodinated poppyseed oil, iodinated sesame oil, iodinated rapeseed oil and brominated olive oil, are effective contrast agents, but are not entirely satisfactory because of their high viscosity, and somewhat irritating properties. They must be injected under pressure and after examination be withdrawn by aspiration, for otherwise they remain largely unabsorbed for a period of years. Cicatrix formation may result from their prolonged irritation from contact with the tissues. Their high viscosity tends to cause separation of the oil into globules, rendering diagnosis difficult. The mixture of ethyl iodophenylundecylates is undoubtedly the best myelographic agent previously produced. It is less viscous than the iodinated glyceride oils and, therefore, is more easily introduced, withdrawn and absorbed. However, it is reported that at least a year is required for complete absorption and elimination of as little as 0.5 to 1.0 cc. in man.

The possibility of using water-soluble radiopaque media as myelographic agents has been investigated, but these compounds have been found unsatisfactory for a number of reasons. Diffusion is too rapid so that the compound quickly becomes diluted with spinal fluid, thereby losing its radiopacity unless a large possibly toxic quantity is injected. Water soluble substances also are rapidly absorbed into the circulatory system creating increased hazards of systemic poisoning.

The alkoxyalkyl iodoalkoxybenzoates have many advantages over the above-described myelographic agents. For instance they are absorbed from the spinal spaces, so they do not have to be removed by aspiration when the radiologic examination is completed. They cause little or no irritation of the spinal membranes. Experimental studies with several compounds within the scope of this invention have shown amounts required for radiologic examination are completely eliminated from the cerebrospinal system of rabbits or cats within ten to twenty-five days, with all but a trace being gone in a few days. Similar experiments in cats and dogs with ethyl iodophenylundecylate showed appreciable amounts remaining in the spinal cord for as long as eight months. Irritation tests in rabbits' eyes showed irritation of the conjunctiva by the latter compound, greater than that shown by the new compounds.

The toxicities of the compounds of my invention orally or intraperitioneally, are low enough

to permit the compounds to be safely used as myelographic agents. The esters of my invention have the advantage of being pure compounds instead of a mixture of isomers. They have a greater radiopacity due to a higher percentage of iodine (from 35 to 40% as compared with 30.5% for ethyl iodophenylundecylate).

Certain members of these alkoxyalkyl iodoalkoxybenzoates when in the pure state may crystallize to form low melting solids. Since myelographic agents must be injected in liquid form and retained so during examination and removal, these solid esters may be rendered permanently fluid by admixture with another member of the series, forming a eutectic mixture with a melting point lower than body temperature.

My new compounds may be synthesized by the esterification of an iodoalkoxybenzoic acid by one of the following methods: (1) the iodoalkoxybenzoic acid and an alkoxyalkanol are combined directly in the presence of an acid catalyst; (2) said acid in the form of a reactive derivative, such as the acid chloride or anhydride, is caused to react with an alkoxyalkanol; or (3) a metallic salt of said acid is caused to react with an alkoxyalkyl halide.

The following examples will illustrate my invention more completely, but should not be construed as a limit to the scope of the invention, this being determined instead by the appended claims.

Example 1

2-ethoxyethyl 3-iodo-4-methoxybenzoate.—A mixture of 27.8 g. of 3-iodo-4-methoxybenzoic acid and 50 cc. of thionyl chloride is heated on a steam bath for one and one-half hours. The unreacted thionyl chloride is then removed at reduced pressure and 50 cc. of 2-ethoxyethanol is added followed by additional heating for a half hour. The mixture is poured into ice-water and the product extracted with ether. The ether extracts are washed with water, dilute sodium carbonate solution and again with water, and dried over anhydrous sodium sulfate. After removal of the ether the product distils at 163–173° C. (0.8–1.3 mm.); yield about 28 g. Redistillation gives a purer sample of 2-ethoxyethyl 3-iodo-4-methoxybenzoate, B. P. 163-165° C. (0.06 mm.), M. P. 50.5–52.5° C.

Example 2

2 - ethoxyethyl 3 - iodo - 4 - ethoxybenzoate.—A mixture of 20 g. of 3-iodo-4-ethoxybenzoic acid, 150 cc. of 2-ethoxyethanol and 2 cc. of concentrated sulfuric acid is refluxed for sixteen hours. Then the mixture is poured into ice water and the product is extracted with ether. The ether extracts are washed with water, dilute sodium carbonate solution and again with water, and dried over sodium sulfate. After removal of the ether, the product, 2-ethoxyethyl 3-iodo-4-ethoxybenzoate, distils at 170–172° C. (0.6 mm.); yield about 23 g., M. P. 63–64° C.

Example 3

2-methoxyethyl 3-iodo-4-ethoxybenzoate is prepared in the manner described in Example 2 using as starting materials 3-iodo-4-ethoxybenzoic and 2-methoxyethanol. It distils at 178–180° C. (1.5 mm.) and has the M. P. 53–53.5° C.

Example 4

3-ethoxypropyl 3-iodo-4-ethoxybenzoate is prepared in the manner described in Example 2 using as starting materials 3-iodo-4-ethoxybenzoic acid and 3-ethoxypropanol. It distils at 184–185° C. (0.8 mm.).

Example 5

2-butoxyethyl 3-iodo-4-methoxybenzoate is prepared in the manner described in Example 2 using as starting materials 3-iodo-4-methoxybenzoic acid and 2-butoxyethanol. It distils at 192–194° C. (0.8 mm.).

Example 6

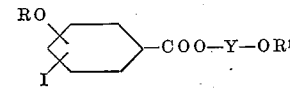
3-methoxypropyl 3-iodo-4-methoxybenzoate is prepared in the manner described in Example 2 using as starting materials 3-iodo-4-methoxybenzoic acid and 3-methoxypropanol. It distils at 171–172° C. (0.8 mm.).

Example 7

2-ethoxyethyl 2-iodo-5-methoxybenzoate is prepared in the manner described in Example 2, using as starting materials 2-iodo-5-methoxybenzoic acid and 2-ethoxyethanol. It distils at 173–175° C. (0.6 mm.).

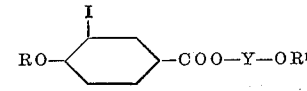
I claim:

1. A compound having the formula



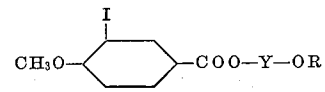
where Y is an alkylene bridge of 2 to 3 carbon atoms and at least two carbon atoms separate the carboxyl group from the —OR^1 group, and R and R^1 are alkyl groups of such a size that the total number of carbon atoms in the molecule does not exceed 16, and wherein the iodine atom is in a position selected from ortho and para with respect to the alkoxy group.

2. A compound having the formula



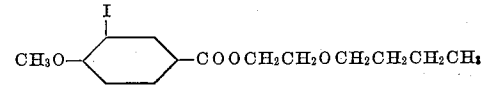
where Y is an alkylene bridge of 2 to 3 carbon atoms and at least two carbon atoms separate the carboxyl group from the —OR^1 group, and R and R^1 are alkyl groups of such a size that the total number of carbon atoms in the molecule does not exceed 16.

3. A compound having the formula

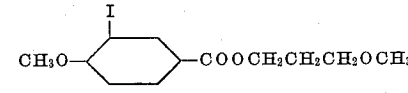


where Y is an alkylene bridge of 2 to 3 carbon atoms and at least two carbon atoms separate the carboxyl group from the OR group, and R is an alkyl group of 1–5 carbon atoms.

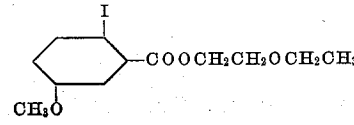
4. 2 - butoxyethyl 3 - iodo - 4 - methoxy - benzoate, having the formula



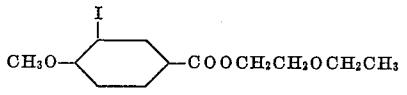
5. 3-methoxypropyl 3-iodo-4-methoxybenzoate, having the formula



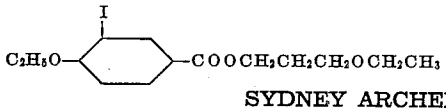
6. 2 - ethoxyethyl 2-iodo-5-methoxybenzoate, having the formula



7. 2 - ethoxyethyl 3 - iodo - 4 - methoxy - benzoate, having the formula



8. 3 - ethoxypropyl 3-iodo-4-ethoxybenzoate, having the formula



SYDNEY ARCHER.

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The following references are of record in the file of this patent:

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Certificate of Correction

Patent No. 2,572,828 October 30, 1951

SYDNEY ARCHER

It is hereby certified that error appears in the printed specification of the above numbered patent requiring correction as follows:

Column 2, line 55, for "intraperitioneally" read *intraperitoneally*; column 3, line 69, for "zoic and" read *zoic acid and*;

and that the said Letters Patent should be read as corrected above, so that the same may conform to the record of the case in the Patent Office.

Signed and sealed this 5th day of February, A. D. 1952.

[SEAL]

THOMAS F. MURPHY,
Assistant Commissioner of Patents.