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ALKYLATED PHENOLIC GLYCOLIC ACIDS

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This invention relates to phenolic-glycolic acids and salts thereof. Various unsubstituted phenolic glycolic acids are already known, such as the monophenoxyacetic acids of unsubstituted di-, tri- and higher hydroxylated benzenes.

In accordance with the instant invention alkylated phenolic glycolic acids are provided, such compounds and their salts having been discovered to possess valuable properties not possessed at all, or had to an insufficient degree, by the already known compounds.

More specifically the compounds of the present invention may be referred to as substituted phenoxy acetic acids wherein the substituted phenyl group contains at least one aliphatic radical and at least one phenolic hydroxy radical. The said hydroxy radical or radicals may be joined to the mentioned phenyl group or to one or more benzene rings joined to the phenyl radical through an aliphatic radical or an alkylidene radical.

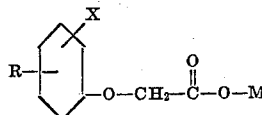
One group of the compounds may be referred to collectively as the mono-phenoxy acetic acids of alkylated polyhydroxy benzenes or the alkyl, hydroxy phenoxyacetic acids. As examples of these compounds there may be mentioned the mono-phenoxy acetic acids of alkylated catechols, resorcinols, hydroquinones, pyrogallols and of other di- and tri-hydroxy benzenes, those compounds being preferred which possess an alkyl radical containing six or more carbon atoms, as the hexyl, octyl, dodecyl and higher radicals. The said radicals may be joined through a primary, a secondary or a tertiary carbon atom and may be a straight chain, a branched chain, or a cycloaliphatic chain.

A second group of compounds within the scope of the present invention may be referred to collectively as mono-phenoxyacetic acids of aliphatic compounds containing two or more phenol groups, or as hydroxy-phenyl-alkyl-phenoxyacetic acids. As examples of this group there may be mentioned the mono-phenoxyacetic acids of the alkylidene-di-phenols in which the alkylidene radical may be a straight, or branched aliphatic group, and of the cycloalkylidene di-phenols, such as the mono-phenoxyacetic acid of cyclohexylidene-(or butylidene- or octylidene-) di-phenols. The alkylidene and cycloalkylidene radicals are hereinafter referred to generically as saturated-hydrocarbonidene radicals. The alkyl or alkylidene radical may be of any practical number of carbon atoms, but preferably also contains at least six carbon atoms.

Included within this second group of com-

pounds are those in which one or more of the benzene rings has attached thereto an additional aliphatic radical of any desirable number of carbon atoms from one up, such as, for example, mono-phenoxy acetic acid of cyclohexylidene-di-o-cresol. Also included are compounds containing more than two phenolic radicals, such as, for instance, tetra-(hydroxy-phenyl)-alkanes in which the alkyl radical may be a straight, a branched or a cycloaliphatic group, such as for example, mono-phenoxy acetic acid of 2,2,5,5-tetra-(hydroxyphenyl)-butane, or -pentane, or -hexane.

By formula, the compounds of the invention broadly considered may be collectively referred to as phenolic glycolic compounds containing one or more aliphatic radicals attached to the phenyl ring of the structure



wherein R is one or several aliphatic radicals (straight, branched, or cyclic chain), and is optional if X contains an aliphatic radical, X either represents one or several phenolic OH groups, or represents an aliphatic radical (straight, branched or cyclic radical) substituted by one or more phenol radicals, and M is an H atom or an atom of a salt-forming metal.

The alkylated phenolic phenoxy acetic acids of the present invention find application as such in industrial processes, but at the present time their most important application arises when they are in the form of their salts. For example, their organic and inorganic salts derived by neutralization with suitable bases, such as sodium or potassium hydroxide, constitute effective water-soluble phenolic soaps. Furthermore, salts having pharmaceutical value, such as bismuth salts and other conventional salts, may be easily prepared from the acids by conventional procedure in which the therapeutic properties already present are retained, due to the presence of the one or more phenolic hydroxy groups in the molecule.

Example 1—Monophenoxyacetic acid of diisobutyl resorcinol

1 mole equivalent of diisobutyl resorcinol, prepared by the process described by the present applicant and co-workers in an article in the Journal of the American Chemical Society, vol. 55, p. 2574 (1933), is dissolved in 1000 cc. of boil-

ing methyl alcohol in a round-bottomed, three-necked flask provided with an efficient stirrer, reflux condenser and dropping funnel. One atomic weight equivalent of metallic sodium is dissolved in a minimum amount (500 cc. methyl alcohol) and this solution is slowly added to the boiling methyl alcohol solution containing the diisobutyl resorcinol. After the addition of the sodium methylate solution has been completed, an additional quantity of methyl alcohol is added sufficient to dissolve any precipitated sodium salt of the diisobutyl resorcinol. One mole equivalent of ethyl chloroacetate is diluted with an equal volume of methyl alcohol, and this solution is then added to the mono-sodium salt of diisobutyl resorcinol. The reaction mixture is then refluxed for from 6 to 8 hours. After this treatment, the reaction mixture is filtered and the alcohol distilled off under subatmospheric pressure and the residue is fractionally distilled under a vacuum to free the phenolic mono-ester from any di-ester which may have been formed in the reaction as a by-product. Separation of these two compounds may alternatively be effected in other ways, as, for example, by dissolving it out of the reaction product or its ether extract with Claisen solution (mixture of equal parts of 50% aqueous potassium hydroxide solution and methyl alcohol). The phenolic phenoxyacetic acid ester is thus taken up by the Claisen solution. The Claisen solution extract from the ether extract is separated from the ether layer and is then acidified with dilute hydrochloric acid. The resulting emulsion is again extracted with ether. The ether extract is dried, filtered, and the ether distilled off. The residue is then crystallized from a diisobutylene solution. The mono-ester obtained is found to have a melting point of 152° C. (uncorrected).

The free acid may be obtained by hydrolyzing the ester in the conventional manner. For this purpose it is not necessary to isolate the desired ester. The Claisen solution extract, as obtained above, may, for example, be refluxed for six hours, after which the methyl alcohol is distilled off, and the residue is dissolved in water. The resulting aqueous solution is filtered and strongly acidified with dilute hydrochloric acid, whereupon the free phenolic phenoxyacetic acid separates out. The free acid may then be recrystallized either from water, ethyl alcohol, or diisobutylene, and leads to a product having a melting point of 215° (uncorrected).

Alternatively, the mono-derivative may be separated from the di-phenoxyacetic acid by hydrolyzing the original reaction mixture by refluxing it after the addition of the ethylchloroacetate and completion of the reaction with an additional amount of sodium methylate solution containing an excess (1½ atomic weight equivalents) of sodium. The methyl alcohol is then distilled off and the residue is subjected to fractional crystallization from water, ethyl alcohol, or diisobutylene.

The same general procedure may be used for producing monophenoxy-acetic acid derivatives of alkylated catechols, hydroquinones and pyrogallols.

Example 2—Mono-phenoxyacetic acid of cyclohexylidene-diphenol

One mole equivalent of cyclohexylidene diphenol, prepared as described by McGreal, Niederl and Niederl, in an article in the Journal of the American Chemical Society, vol. 61, p. 345 (1939),

is introduced into a round-bottomed three-necked flask provided with a reflux condenser, stirrer, and a dripping funnel, and is dissolved in 1000 cc. of boiling methyl alcohol. To this solution is added 500 cc. of methyl alcohol containing one mole equivalent of sodium methylate. Sufficient methyl- or ethyl alcohol, or dioxane, is added to the reaction mixture to effect the solution of any mono-sodium salt which may precipitate out. After this addition, one mole equivalent of ethylchloroacetate dissolved in an equal amount of methyl alcohol is slowly added, and the mixture refluxed for at least 12 hours, or until the reaction is complete, as indicated by the quantity of sodium chloride formed. The resulting product is then treated and purified by a procedure which is similar to that of Example 1. The melting point of the free phenolic monophenoxyacetic acid obtained is 103° C. (uncorrected).

Example 3—Monophenoxyacetic acid of cyclohexylidene-di-o-cresol

Cyclohexylidene-di-o-cresol is treated substantially in accordance with the procedure described in Example 2. The free acid product obtained is found to have a melting point of 125° C. (uncorrected).

Example 4—Monophenoxyacetic acid of 2,2,5,5-tetra (hydroxyphenyl) hexane

One mole equivalent of 2,2,5,5-tetra (hydroxyphenyl) hexane, prepared by condensing one mole of acetonyl acetone (B. P. 190–193° C.) with 4 moles of phenol in the presence of dry hydrogen chloride in a manner described by the present applicant and coworkers in an article in the Journal of the American Chemical Society, vol. 61, pp. 345, 348, 1785 (1939), is dissolved in 200 cc. of methyl alcohol.

Five hundred cc. of methyl alcohol containing one mole equivalent of sodium methylate are then slowly added to the above solution. After completion of the addition, sufficient methyl alcohol, or dioxane, is added to effect complete solution of any precipitated sodium salt. While the reaction mixture is boiling, one mole equivalent of ethylchloroacetate diluted with an equal volume of methyl alcohol is slowly added. The reaction mixture is refluxed for at least 12 hours, or until one mole equivalent of sodium chloride has precipitated out. The solution is then filtered and the methyl alcohol removed by distillation under subatmospheric pressure. The residue is dissolved in a minimum amount of ethyl alcohol or glacial acetic acid and allowed to crystallize, the crude monophenoxyacetic acid of the tetraphenol being further purified by repeating the above crystallization procedure. The free polyphenolic monophenoxyacetic acid has a melting point above 360° C.

As additional examples of compounds within the scope of the present invention, there may be mentioned the mono-phenoxyacetic acids of $\alpha,\alpha,\gamma,\gamma$ -tetra-methobutyl-catechol, or -resorcinol, or -hydroquinone, or -pyrogallol; also the monophenoxyacetic acids of methyl (or ethyl or propyl, etc.) hexylidene-di-phenols, or -di-o-cresols.

The above mentioned tetraphenols and other tetraphenols suitable for use in the practice of the instant process are disclosed in my co-pending patent application Serial No. 333,997, filed May 8, 1940.

In its broadest aspects, the instant invention contemplates naphtholic derivatives similar to the derivatives of phenol herein specifically de-

scribed. Likewise, it includes glycolic acid radicals other than acetic, such as contained in monophenoxy propionic acid and mononaphthoxy butyric acids. Furthermore, the aliphatic radical or chain substituted on the phenolic radical may be interrupted by oxygen, sulfur or nitrogen atoms.

It should be understood that the invention is not limited to the specific examples set out herein, but that it extends to all equivalent materials and structural alterations which will occur to those skilled in the art upon consideration of the instant disclosure and the scope of the claims appended hereto.

I claim:

1. Monoglycolic acid ethers of cyclohexylidene di-phenols.
2. Monoglycolic acid ethers of cyclohexylidene di-o-cresol.
3. Monoglycolic acid ethers of cyclohexylidene di-phenols in which the phenolic rings are substituted by at least one additional aliphatic radical.
4. Monoglycolic acid ethers of cyclohexylidene di-o-cresol in which the phenolic rings are substituted by at least one additional aliphatic radical.

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