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QUINOLINE DISULFIDES

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1 Claim. (Cl. 260—288)

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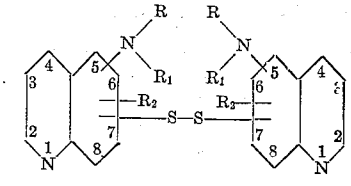
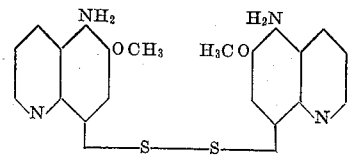
This invention relates to organic compounds and more particularly to quinoline disulfides.

The compounds of this invention may be represented by the following symmetrical formula:



wherein R represents hydrogen, phenyl, benzyl, phenethyl radicals, alkyl radicals having from 1 to 6 carbon atoms, or dialkyl amino alkyl radicals whose alkyl groups have from 1 to 6 carbon atoms; R_1 represents hydrogen, benzoyl radicals or aliphatic acyl radicals having from 1 to 6 carbon atoms; and R_2 represents hydrogen, halogen, hydroxy, methoxy, ethoxy radicals, or alkyl radicals having from 1 to 6 carbon atoms. In the above formula the substituents may be located in any one of the positions 2, 3, 4, 5, 6, 7, and 8 on each quinoline ring, there being no more than one substituent at any of these positions at any one time.

The compounds of our invention are aminodiquinolyl disulfides wherein the amino group itself may be substituted and additionally, other groups, described as R_2 above, may be substituted on the quinoline rings. It is to be noted however that the compounds are symmetrical. For example, if an amino group occupies a position 5 on one quinoline ring it must be correspondingly located on the other ring, and this symmetry applies to all substituents. For example, in 5,5'-diamino-6,6'-dimethoxy-8,8'-diquinolyl disulfide, which may be represented by the following formula:



it will be seen that the molecule is symmetrical and its symmetry is indicated in the nomenclature by the use of prime numbers, these prime numbers indicating the same relative position in the second quinoline ring as in the first quinoline ring.

The compounds of our invention are substantially stable compounds in that they are not readily decomposed under ordinary conditions. However, they may be reduced by strong reducing agents to yield the corresponding thiols. In such reduction reaction, the sulfur-to-sulfur bond is broken and a hydrogen atom combines with each sulfur atom. On the other hand, under the action

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of strong oxidizing agents, the compounds of our invention may be oxidized to sulfinic or sulfonic acids, provided that the amino groups are protected by certain substituents, for example, acetyl groups, in order to prevent attack of the oxidizing agent at the position of the amino groups on the quinoline rings.

The compounds of this invention possess basic properties, conferred by the basic tertiary nitrogens in the quinoline rings. The basicity is further increased if the amino groups are unsubstituted by acyl groups. Being basic, our compounds can readily form soluble acid addition salts such as the hydrochloride, the hydrobromide, and the sulfate. Additionally, insoluble acid addition salts may be prepared, such as the ortho benzoylbenzoate and the dicyclohexyl sulfamate. In such acid addition salts the acids combine with the two nitrogens of the quinoline nuclei, and also with the two amino groups when the latter are unsubstituted by acyl groups.

We may prepare our compounds in various ways. It is convenient, however, to use certain halogen substituted compounds as starting materials in the synthesis. Thus, a substituted aminoquinoline halide may be reacted with a metal disulfide whereby the halogen atom in the quinoline nucleus is substituted by sulfur. We may also prepare the compounds of our invention by reacting the substituted aminoquinoline halide with a metal hydrosulfide to obtain a substituted quinoline thiol which subsequently may be oxidized, by air or some other mild oxidizing agent, to the substituted diquinolyl disulfide.

When a substituted quinoline halide is used as a starting material in preparing the above compounds, it should be noted that the halogen atom when located at any one of the positions 3, 5, 6, 7, and 8 of the quinoline nucleus is relatively inactive and will not readily react with metal hydrosulfides or metal disulfides. It is therefore desirable to locate within the molecule some group which has an activating effect upon the halogen. Among groups which may be used for this purpose is the nitro group which when located in a position ortho or para to the halogen atom has an activating effect on the halogen causing it to react much more readily thereby making it more amenable to replacement. The presence of the nitro group thus may serve two purposes, namely, activating the halogen, and supplying the nitrogen for the amino group. However, the nitro group used for the activation of the halogen need not be the source of the amino group. The nitro group may be replaced by chemical conversions to one of the groups which comprise R_2, or after having served its purpose as an activating agent may be completely removed from the quinoline ring by chemical means.

When the halogen is located in either of the positions 2 or 4 on the quinoline nucleus, it is sufficiently reactive so that no activating group is required.

An amino group which may be protected by some substituent may be present in the halogen substituted molecule before reaction of the substituted quinoline halide with a metal hydrosulfide or a metal disulfide, and after the reaction has been carried out, it is a matter of choice whether the amino group should be left protected or the protecting group removed to liberate the free amino group. It may be noted however that the requirement for an activating group in case the halogen atom is located at any one of the points 3, 5, 6, 7, or 8 in the quinoline ring is not eliminated by the presence of an amino group or a substituted amino group. It is only when the halogen is in the 2 or 4 position of the quinoline ring that an activating group is unnecessary.

Among nitro compounds suitable for the synthesis of compounds of this invention in accordance with the generalizations given above may be mentioned the following, which are listed with accompanying literature references:

5-chloro-6-methoxy-8-nitroquinoline, Ann. Inst. Pasteur 44, 719

5-chloro-8-nitroquinoline, Bull. Soc. Chim. 47, 571 (1930)

2-chloro-6-nitroquinoline, J. Prakt. Chem. 93, 381 (1916)

2-chloro-5-nitroquinoline, J. Prakt. Chem. 93, 383, (1916)

2-chloro-8-nitroquinoline, J. Prakt. Chem. 93, 376 (1916)

8-chloro-5-nitro-2, 4-dimethylquinoline, J. Chem. Soc. 1927, 1932

5-bromo-6-nitroquinoline, Rec. Trav. Chim. 48, 550 (1929)

6-chloro-5-nitroquinoline, Bull. Soc. Chim. 47, 738 (1930)

6-chloro-7-nitroquinoline, Bull. Soc. Chim. 47, 738 (1930)

7-chloro-6-nitroquinoline, Bull. Soc. Chim. 47, 738 (1930)

2-chloro-8-nitro - 6 - methylquinoline, J. Chem. Soc. (1931) 2195

7-chloro-8-nitroquinoline, Ann. Inst. Pasteur 44, 719 (1930)

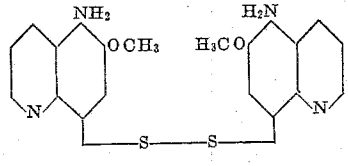
2-chloro-6-nitro - 4 - methylquinoline, J. Chem. Soc. (1930) 2346

2-chloro-3-nitro-4-chloroquinoline, Ber. 51, 1500

The following examples illustrate compounds of our invention and methods of preparing the same.

Example 1

5,5'-diamino-6,6'-dimethoxy-8,8'-diquinolyl disulfide, represented by the formula



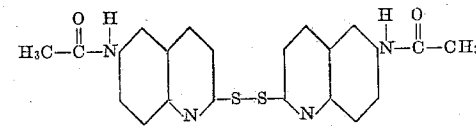
may be prepared by reacting 5-nitro-6-methoxy-8-chloroquinoline with sodium disulfide to produce 5,5'-dinitro - 6,6-dimethoxy - 8,8'-diquinolyl disulfide, and reducing the nitro groups of the 5,5' - dinitro-6,6'-dimethoxy-8,8' - diquinolyl disulfide to produce the desired compound in the manner indicated below:

20 g. of 5-nitro-6-methoxy-8-chloroquinoline are dissolved in about 250 cc. of alcohol. This solution is refluxed, and 5.5 g. of sodium disulfide, dissolved in a minimum amount of water, are added slowly. The refluxing is continued for two hours, the bulk of the alcohol removed by evaporation in vacuo, and the residue treated with an excess of water, whereupon a precipitate of a nitro compound, namely 5,5' - dinitro-6,6'-dimethoxy-8,8'-diquinolyl disulfide separates.

3 g. of the nitro compound, 5,5'-dinitro-6,6'-dimethoxy-8,8'-diquinolyl disulfide, are added to a solution of 12 g. of stannous chloride dissolved in 30 cc. of hydrochloric acid and the solution heated at about 80° C. for about one half hour. Upon cooling to about 0° C., a precipitate of the tin double salt of 5-amino-6-methoxy-8-quinolyl thiol separates. This precipitate is filtered off, is treated with about 25 cc. of 50 percent sodium hydroxide solution, and diluted to about 150 cc. with water. About 10 g. of sodium bisulfite are then added to the solution and air passed through the solution, whereupon a precipitate of the desired 5,5'-diamino-6,6'-dimethoxy-8,8'-diquinolyl disulfide forms.

Example 2

6,6' - diacetylamino - 2,2' - diquinolyl disulfide, with the following formula

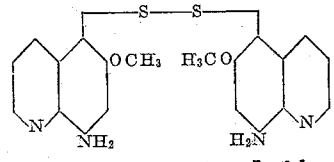


may be prepared by reacting 2-chloro-6-acetylaminoquinoline with sodium disulfide in the following manner:

22 g. of 2-chloro-6-acetylaminoquinoline and 5.5 g. of sodium disulfide dissolved in about 250 cc. of 90 percent alcohol are refluxed for about six hours. The bulk of the alcohol is then removed in vacuo and the residual solution treated with about 100 cc. of water and cooled to about 0° C. A precipitate of the desired 6,6'-diacetylamino-2,2'-diquinolyl disulfide separates.

Example 3

6,6'-dimethoxy - 8,8' - diamino-5,5'-diquinolyl disulfide, with the following formula

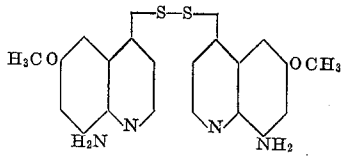


may be prepared by reacting 5-chloro-6-methoxy-8-nitroquinoline with sodium disulfide to form 6,6' - dimethoxy-8,8'-dinitro-5,5'-diquinolyl disulfide and reducing the nitro groups of the 6,6'-dimethoxy-8,8'-dinitro-5,5'-diquinolyl disulfide to produce the desired compound. Thus, 21 g. of 6-methoxy-8-amino-5-quinoline thiol are dissolved in about 250 cc. of alcohol, and this solution refluxed. 5.5 g. of sodium disulfide, dissolved in a minimum amount of water, are added slowly. The refluxing is continued for two hours, the bulk of the alcohol removed by evaporation in vacuo, and the residue treated with an excess of water, whereupon a precipitate of 6,6'-dimethoxy-8,8'-diamino-5,5'-diquinolyl disulfide separates. 3 g. of this 6,6'-dimethoxy-8,8'-diamino-5,5'-diquinolyl disulfide are added to a solution of 12 g. of stannous chloride dissolved in 30 cc. of hydrochloric acid and the solution heated at

about 80° C. for about one half hour. Upon cooling to about 0° C. a precipitate of the tin double salt of 6-methoxy-8-amino-5-quinoline thiol separates. This precipitate is filtered off, treated with about 25 cc. of 50 percent sodium hydroxide solution, and diluted to about 150 cc. with water. About 10 g. of sodium bisulfite are then added to the solution and air passed through the solution, whereupon a precipitate of 6,6'-dimethoxy-8,8'-diamino-5,5'-diquinolyl disulfide forms.

Example 4

6,6'-dimethoxy-8,8'-diamino - 4,4' - diquinolyl disulfide with the following formula



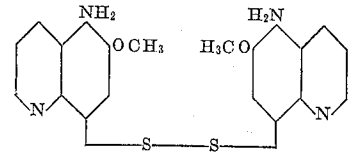
may be prepared by reacting 4-chloro-6-methoxy-8-aminoquinoline with sodium disulfide in the following manner:

20 g. of 4-chloro-6-methoxy-8-aminoquinoline and 5.5 g. of sodium disulfide are dissolved in about 250 cc. of 90 percent alcohol and the resulting solution refluxed for about six hours. The bulk of the alcohol is removed in vacuo and the residual solution treated with about 100 cc. of

water and cooled to about 0° C. A precipitate of the desired 6,6'-dimethoxy-8,8'-diamino-4,4'-diquinolyl disulfide separates upon cooling of the solution.

We claim as our invention:

5,5'-diamino-6,6'-dimethoxy - 8,8' - diquinolyl disulfide having the following formula:



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