

3-ARYLMERCAPTO-4-QUINALDINECARBOXYLIC ACIDS

A THESIS

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In Partial Fulfillment

of the Requirements for the Degree

Master of Science in Chemistry

by

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3-ARYLMERCAPTO-4-QUINALDINECARBOXYLIC ACIDS

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Date approved by chairman May 21, 1948

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F. X. W.

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CHAPTER I
THE PFITZINGER REACTION

3-ARYLMERCAPTO-4-QUINALDINECARBOXYLIC ACIDS

CHAPTER I

THE PFITZINGER REACTION

Pfizzinger was the first worker to condense an isatin compound with a ketone to form a quinaldinecarboxylic acid.^{1,2} The general reaction between isatins and ketones now bears his name.

The Pfizzinger reaction has been extended by workers in this laboratory to include the condensation of aryloxyketones, arylthioketones, and alkoxyaryloxyketones with isatins.^{3,4,5,6,7,8}

The chief product of the reaction of isatins with unsymmetrical ketones will normally have the larger group in the 3-position.^{9,10}

¹Pfizzinger, J. prakt. Chem., 33, 100 (1886)

²Pfizzinger, J. prakt. Chem., 38, 584 (1888)

³Calaway and Henze, J. Am. Chem. Soc., 61, 1355 (1939)

⁴Knight, Porter, and Calaway, J. Am. Chem. Soc.,
66, 1893 (1944)

⁵Newell and Calaway, J. Am. Chem. Soc., 69, 116 (1947)

⁶Dowell, McCullough, and Calaway, J. Am. Chem. Soc.,
70, 226 (1948)

- ⁷Sublett and Calaway, J. Am. Chem. Soc., 70, 674 (1948)
- ⁸McCullough, Georgia School of Technology,
Master's Thesis (1948)
- ⁹Pfizzinger, J. prakt. Chem., 56, 283 (1897)
- ¹⁰Von Braun, Gmelin, and Schulthesis, Ber., 56 1344 (1923)

CHAPTER II
THE PURPOSE OF THIS INVESTIGATION

CHAPTER II

THE PURPOSE OF THIS INVESTIGATION

Experiments have proved the activity of the quinoline group in contributing to the chemotherapeutic effectiveness of various medicinal agents, particularly in the anti-malarial properties of quinine. Other substituted quinoline compounds which have been utilized in chemotherapy are plasmochen, cinchophen, and atoquinol. The compounds reported in this thesis are all substituted cinchoninic acids and are therefore members of this same class.

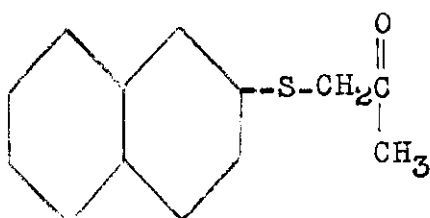
Arylmercaptopropanones are readily available from chloroacetone and the thiocresols and thionaphthols. The tolylmercaptopropanones have already been condensed with certain of the isatins by Newell and Calaway⁵ and the work reported herein is an extension of their efforts.

CHAPTER III
EXPERIMENTAL

CHAPTER III

EXPERIMENTAL

The preparation of 1-(β -naphthylmercapto)-2-propanone (I)



(I)

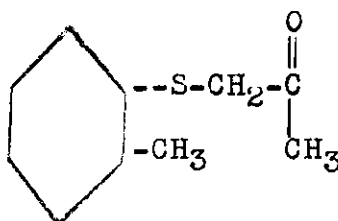
1-(β -Naphthylmercapto)-2-propanone (I) was prepared from chloroacetone and β -thionaphthol by the method used by Newell and Calaway⁵ to prepare the tolylmercaptopropanones.

Thirty two grams (0.2 mole) of β -thionaphthol and two hundred cc. of toluene were mixed in a 500-ml., three-necked, round-bottomed flask equipped with a mechanical stirrer and a condenser fitted with a drying tube.

Four and six-tenths grams (0.2 mole) of finely divided sodium metal was added over a period of thirty minutes. The reaction mixture was heated on a steam bath for two hours to insure complete reaction. The white solid sodium salt of β -thionaphthol settled out.

Eighteen and five-tenths grams (0.2 mole) of chloroacetone was dropped in over a period of fifteen minutes and the mixture was heated on a hot water bath for two hours. The solid sodium chloride formed in the reaction was removed by filtration. The toluene used as a solvent for the reaction was removed by distillation under reduced pressure and on cooling 1-(β -naphthylmercapto)-2-propanone solidified. The product was purified by recrystallization from cyclohexane and was found to be a light tan-colored solid.

The Preparation of 1-(o-Tolylmercapto)-2-propanone (II)



(II)

The tolylmercaptopropanones were prepared by the method of Newell and Calaway.⁵

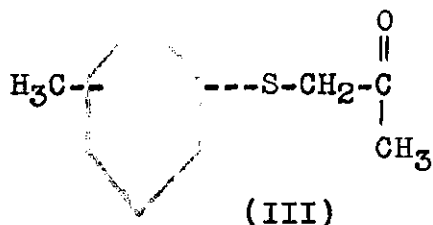
Twenty-five grams (0.2 mole) of o-thiocresol and 200 ml. of toluene were mixed in a 500 ml., three-necked, round-bottomed flask fitted with a mechanical stirrer, dropping funnel, and reflux condenser with calcium chloride drying tube attached.

Four and six-tenths grams (0.2 mole) of finely divided sodium metal was added over a period of thirty minutes and the mixture was heated on a steam bath for a period of two hours. The contents of the flask were allowed to cool and then 18.5 grams (0.2 mole) of chloroacetone was dropped in over a period of ten minutes and the mixture was heated on a hot water bath for one and one-half hours.

The toluene used as a solvent was removed by distillation under reduced pressure and the crude product, 1-(o-tolylmercapto)-2-propanone, was an amber liquid. The yield of the crude product was 54 per cent (19.4 grams).

The pure product obtained by Newell and Calaway⁵ was described as a pale yellow liquid boiling at 138° (8mm.).

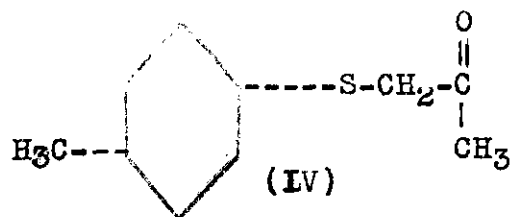
The Preparation of 1-(m-Tolylmercapto)-2-propanone (III)



This compound was prepared by the method outlined for 1-(o-tolylmercapto)-2-propanone (II) but was obtained in higher yield (crude), 71.5 per cent of the theoretical amount.

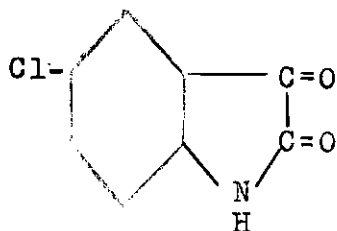
Newell and Calaway⁵ reported a boiling point of 142° (8mm.) for 1-(m-tolylmercapto)-2-propanone and described it as a pale yellow liquid.

The Preparation of 1-(p-Tolylmercapto)-2-propanone (IV)



This compound was prepared by the method described for the o-isomer. The yield of the crude product was 25.5 grams (71 per cent of the theoretical amount).

1-(p-tolylmercapto)-2-propanone is described in the literature⁵ as a pale yellow liquid boiling over the range 133-135° (7-9 mm.).

The Preparation of 5-Chloroisatin¹¹ (V)

(V)

Ninety grams (0.54 mole) of chloral hydrate was dissolved in 1200 ml. of water in a five-liter, round-bottomed flask, and 1300 grams of crystalline sodium sulfate was added. A solution of 63.75 grams (0.5 mole) of p-chloroaniline in 300 ml. of water and 43 ml. (0.52 mole) of concentrated hydrochloric acid was added to the chloral hydrate solution, and this was followed by 110 grams (1.58 moles) of hydroxylamine hydrochloride in 500 ml. of water. The contents of the flask were then heated over a Meeker burner at such a rate to produce vigorous boiling in approximately forty-five minutes. The liquid was allowed to boil for two minutes, and on cooling, solid p-chloro-isonitrosoacetanilide crystallized out. This product was separated by filtration.

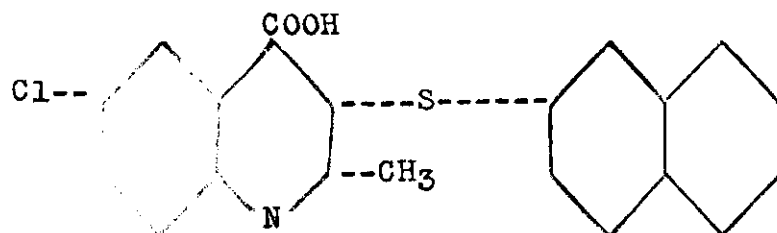
Six hundred grams (326 ml.) of concentrated sulfuric acid was warmed to 50 degrees in a one-liter, three-necked flask fitted with a mechanical stirrer and the p-chloro-isonitrosoacetanilide was added with stirring at such a rate as to keep the temperature between 50 and 60 degrees. After the addition of the isonitroso compound was complete, the solution was allowed to heat to 80 degrees and kept at this temperature

¹¹Gilman, Organic Synthesis-Collective Vol. I p. 321

until the tendency to heat up ceased (about twenty minutes). The reaction mixture was cooled to room temperature, poured over ten times its volume of cracked ice, and allowed to stand until the ice melted. The crude 5-chloroisatin which separated out was filtered and washed free of sulfuric acid with cold water.

The product was purified by suspending it in one liter of hot water and adding to the suspension a solution of 88 grams of sodium hydroxide in 200 ml. of water; this was sufficient to take the product into solution. Dilute hydrochloric acid (1:2) was added until a slight precipitate formed. The solution was immediately filtered, the precipitate rejected, and the filtrate made acid to congo red paper with dilute hydrochloric acid. The solution was then cooled rapidly in an ice bath, the 5-chloroisatin filtered off and dried in air. The pure product was orange in color, and was obtained in a yield of 56 grams (62 per cent of the theoretical amount).

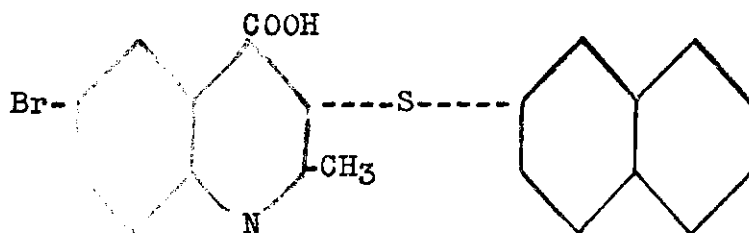
The Preparation of 6-Chloro-3-(β -Naphthylmercapto)-
4-quinaldinecarboxylic Acid (VI)



Nine and one-tenth grams (0.05 mole) of 5-chloroisatin was dissolved in 130 ml. of 33 per cent potassium hydrxide solution and placed in a three-necked, round-bottomed flask fitted with a mechanical stirrer and reflux condenser. Ten and eight-tenths grams (0.05 mole) of 1-(β -naphthylmercapto)-2-propanone was added and the mixture was heated on a steam bath for two and one-half hours. The potassium salt of the desired acid formed as a solid when the above mixture was cooled; the solid was dissolved in hot water, boiled with Nuchar for five minutes, filtered hot, and again treated with Nuchar. After being filtered again, the hot solution was acidified with 1;1 acetic acid and cooled in an ice bath, causing the precipitation of 6-chloro-3-(β -naphthylmercapto)-4-quinaldinecarboxylic acid.

The product thus obtained was a light yellow solid. The yield was 8.7 grams, 45.8 per cent of the theoretical amount. A quantitative nitrogen determination gave a value of 3.77 per cent, as compared with the theoretical percentage of 3.67.

The Preparation of 6-Bromo-3-(β -Naphthylmercapto)-
4-quinaldinecarboxylic Acid (VII)



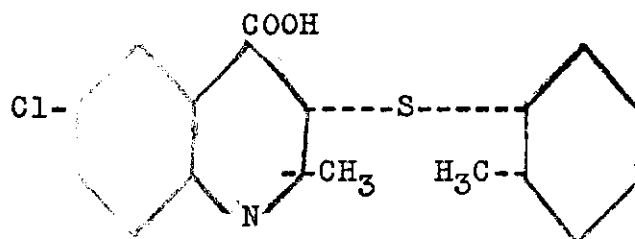
(VII)

This compound was prepared by the method outlined for the corresponding chloro-derivative, using 5-bromoisatin prepared in this laboratory by workers using the general procedure outlined in Organic Synthesis.¹¹

6-Bromo-3-(β -naphthylmercapto)-4-quinaldinecarboxylic was obtained in a yield of 40.1 per cent of the theoretical amount (8.9 grams).

Analysis of a sample previously dried over phosphorus pentoxide gave a nitrogen content of 3.78 per cent. The calculated value is 3.28 per cent.

The Preparation of 6-Chloro-3-(*o*-tolylmercapto)-
4-quinaldine carboxylic acid (VIII)



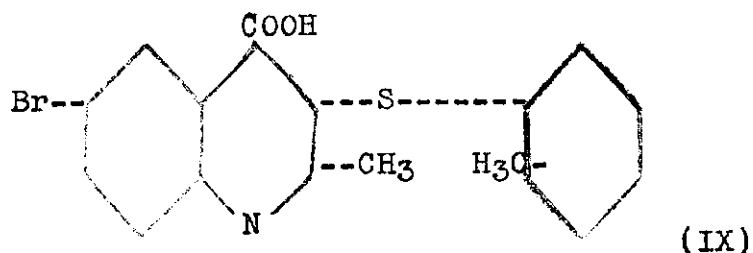
(VIII)

The method used in the preparation of this compound was the same general procedure that was used in the preparation of the *o*-naphthylmercapto derivative. Nine and eight-tenths grams (0.054 mole) of 5-chloroisatin was dissolved in 130 ml. of 33 per cent potassium hydroxide solution and placed in a three-necked, round-bottomed flask fitted with a mechanical stirrer and reflux condenser. Nine and seven-tenths grams (0.054 mole) of *o*-tolylmercaptopropanone was added and the mixture was heated with stirring for a period of one hour.

The liquid portion of the above mixture was removed by decantation and the solid potassium salt was dissolved in hot water and twice treated with Nuchar. The quinaldinecarboxylic acid was precipitated from the hot solution by acidification with acetic acid (1:1).

A yield of 8.1 grams (44 per cent of the theoretical amount) was obtained for the 6-chloro-3-(*o*-tolylmercapto)-4-quinaldinecarboxylic acid. The observed nitrogen content was 4.31 per cent, as compared with the calculated value of 4.08 per cent.

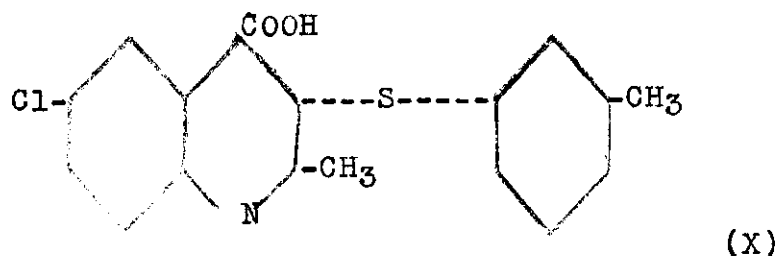
The Preparation of 6-Bromo-3-(*o*-tolylmercapto)-
4-quinaldinecarboxylic acid (IX)



This compound was prepared by the same method as that outlined for the preparation of the corresponding chloro-derivative. 6-Bromo-3-(*o*-tolylmercapto)-4-quinaldinecarboxylic acid was obtained in a yield of 10.1 grams, corresponding to 48.5 per cent of the theoretical amount.

A nitrogen analysis gave a value of 3.66 per cent. The theoretical amount is 3.61 per cent.

The Preparation of 6-Chloro-3-(m-tolylmercapto)-
4-quinaldinecarboxylic acid (X)

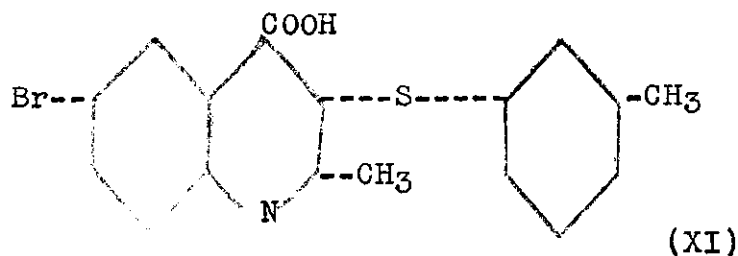


Thirteen and two-tenths grams (0.072 mole) of 5-chlorosisatin was dissolved in 150 ml. of 33 per cent potassium hydroxide solution and placed in a 500 ml., three-necked, round-bottomed flask fitted with mechanical stirrer and reflux condenser. Twelve and nine-tenths grams of 1-(m-tolylmercapto)-2-propanone was added and the mixture was heated on a steam bath for a period of one and one-half hours.

The liquid portion was removed by filtration and the solid potassium salt was dissolved in hot water and twice treated with Nuchar. The hot solution was acidified with acetic acid (1:1), causing the formation of the light tan precipitate of 6-chloro-3-(m-tolylmercapto)-4-quinaldinecarboxylic acid.

A yield of 12.7 grams (51.7 per cent of the theoretical) was obtained in this preparation. A quantitative nitrogen determination gave a value of 4.34 per cent as compared with the calculated value, 4.08 per cent.

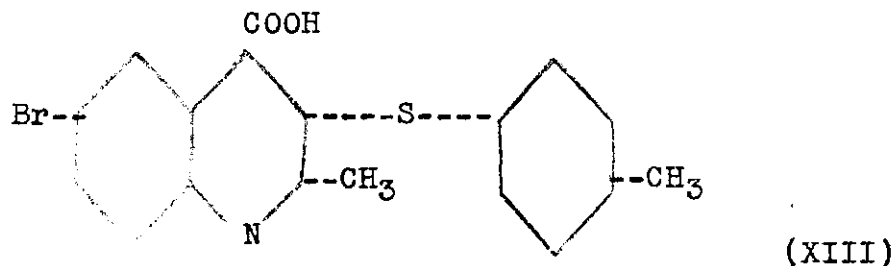
The Preparation of 6-Bromo-3-(m-tolylmercapto)-4-quinolinecarboxylic acid (XI)



This compound was prepared by the method outlined for the preparation of the corresponding chloro-derivative. A yield of 20.2 grams, corresponding to 73.7 per cent of the theoretical amount, was obtained.

Analysis of a sample previously dried over phosphorus pentoxide gave a nitrogen content of 4.03 per cent. The theoretical amount is 3.61 per cent.

The Preparation of 6-Bromo-3-(p-tolylmercapto)-
4-quinaldinecarboxylic acid (XIII)



6-Bromo-3-(p-tolylmercapto)-4-quinaldinecarboxylic acid was prepared by the same general procedure as the chloro-derivative. The yield was 18.5 grams, corresponding to 67.6 per cent of the theoretical amount.

A quantitative nitrogen analysis of a sample previously dried over phosphorus pentoxide gave a result of 3.73 per cent. The calculated value is 3.61 per cent.

CHAPTER IV
DISCUSSION OF RESULTS

CHAPTER IV

DISCUSSION OF RESULTS

The preparation of arylthioketones by the method of Newell and Calaway⁵ has been extended to include 1-(*S*-naphthylmercapto)-2-propanone. This compound is a light tan solid, while the tolylmercaptopropanones are pale yellow liquids.

These thioketones have been utilized in the synthesis of eight new substituted quinoline acids from chloro- and bromoisatin. It was found that the time required for the condensation of the ketones with these isatin derivatives was less than that reported as necessary for the completion of reactions with methylisatin.⁸

The highest yield (73.7 per cent) was obtained in the preparation of 6-bromo-3-(*p*-tolylmercapto)-4-quinaldine-carboxylic acid (XII) and the lowest (40.1 per cent) in the preparation of 6-bromo-3-(*S*-naphthylmercapto)-4-quinaldine-carboxylic acid (VII).

No sharp melting point could be determined for any of the compounds. The colors of all the acids darkened in the range 180-190° and decarboxylation occurred at slightly higher temperatures.

The quinoline acids all showed a tendency to hold water of crystallization. This water was removed by drying the samples in a desiccator over phosphorus pentoxide.

The potassium salts of all the quinaldinecarboxylic acids

prepared possess soap-like properties. They tend to foam in aqueous solution and are salted out by high concentrations of potassium hydroxide.

CHAPTER V

SUMMARY

CHAPTER V

SUMMARY

The following compounds have been prepared and a study made of some of their properties:

1. Ketones

1-(β -Naphthylmercapto)-2-propanone (I);

1-(o-Tolylmercapto)-2-propanone (II);

1-(m-Tolylmercapto)-2-propanone (III);

1-(p-Tolylmercapto)-2-propanone (IV).

2. Substituted Quinoline Acids

6-Chloro-3-(β -naphthylmercapto)-4-quinaldinecarboxylic acid (VI); 6-Bromo-3-(β -naphthylmercapto)-4-quinaldinecarboxylic acid; 6-Chloro-3-(o-tolylmercapto)-4-quinaldinecarboxylic acid (VIII);

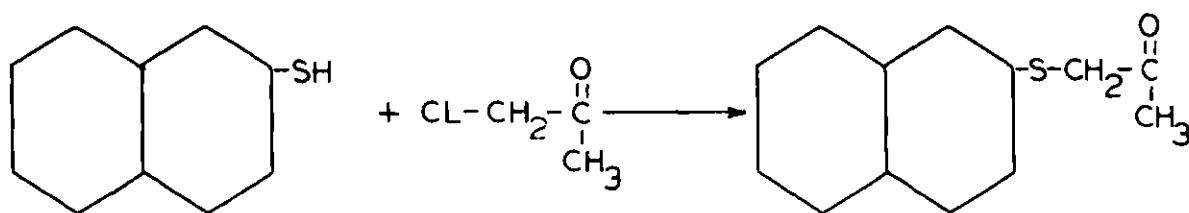
6-Bromo-3-(o-tolylmercapto)-4-quinaldinecarboxylic acid (IX); 6-Chloro-3-(m-tolylmercapto)-4-quinaldinecarboxylic acid (X); 6-Bromo-3-(m-tolylmercapto)-4-quinaldinecarboxylic acid (XI);

6-Chloro-3-(p-tolylmercapto)-4-quinaldinecarboxylic acid (XII); 6-Bromo-3-(p-tolylmercapto)-4-quinaldinecarboxylic acid (XIII).

APPENDIX

FIGURE 1

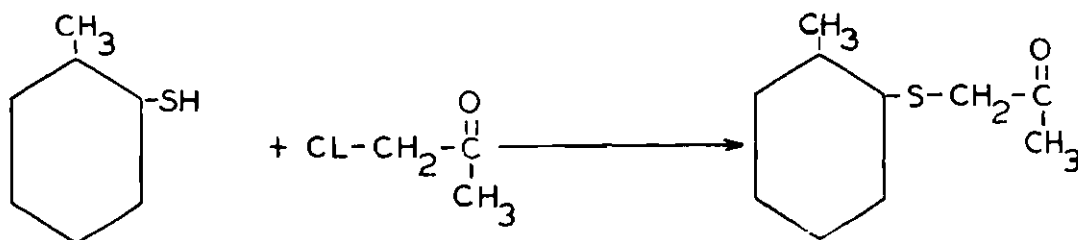
THE PREPARATION OF 1-[B-NAPHTHYLMERCAPTO]-2-
PROPANONE [I]



[I]

FIGURE 2

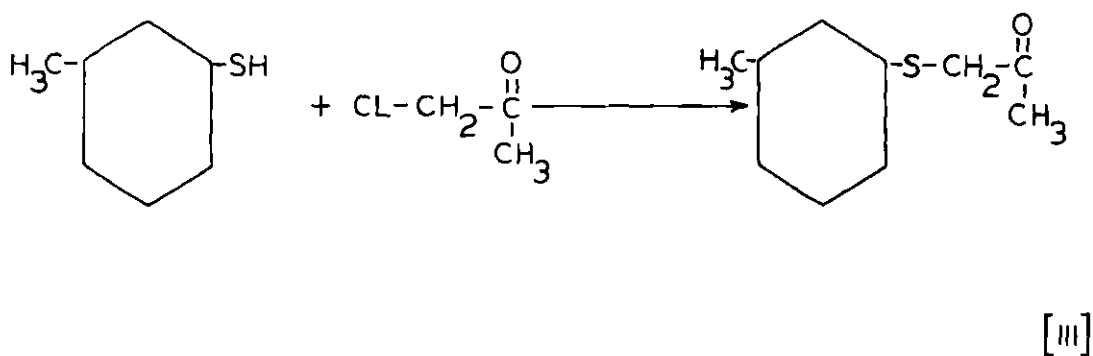
THE PREPARATION OF 1-[O-TOLYLMERCAPTO]-2-
PROPANONE [II]



[II]

FIGURE 3

THE PREPARATION OF 1-[M-TOLYLMERCAPTO]-2-
PROPANONE [III]

FIGURE 4

THE PREPARATION OF 1-[P-TOLYLMERCAPTO]-2-
PROPANONE [IV]

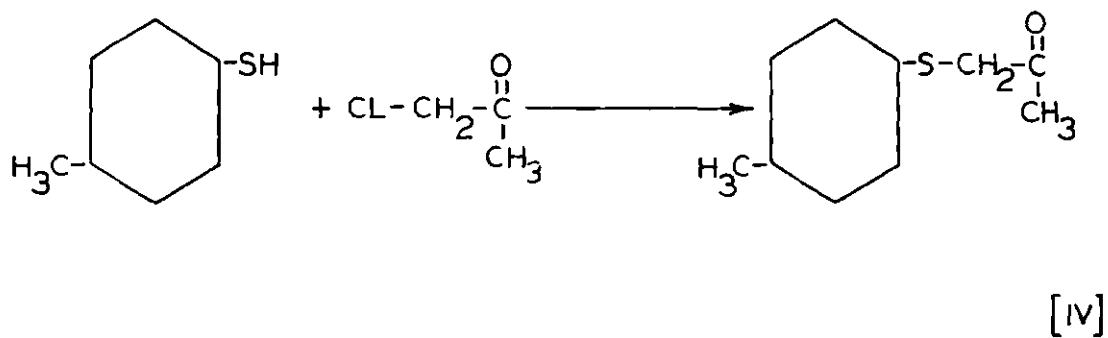
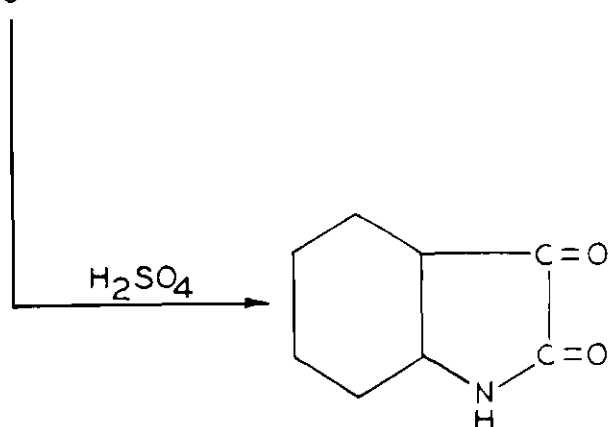
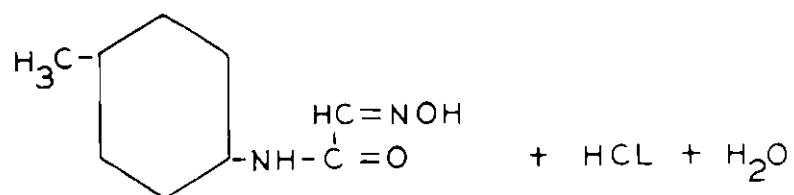
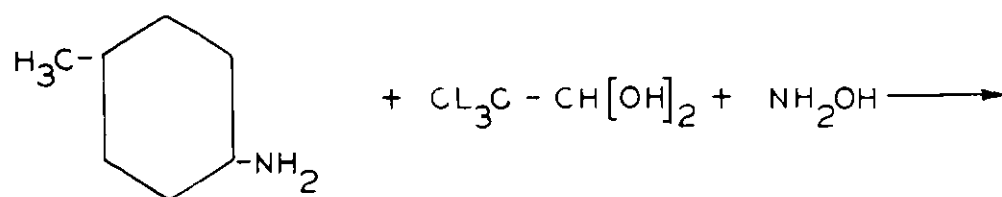


FIGURE 5

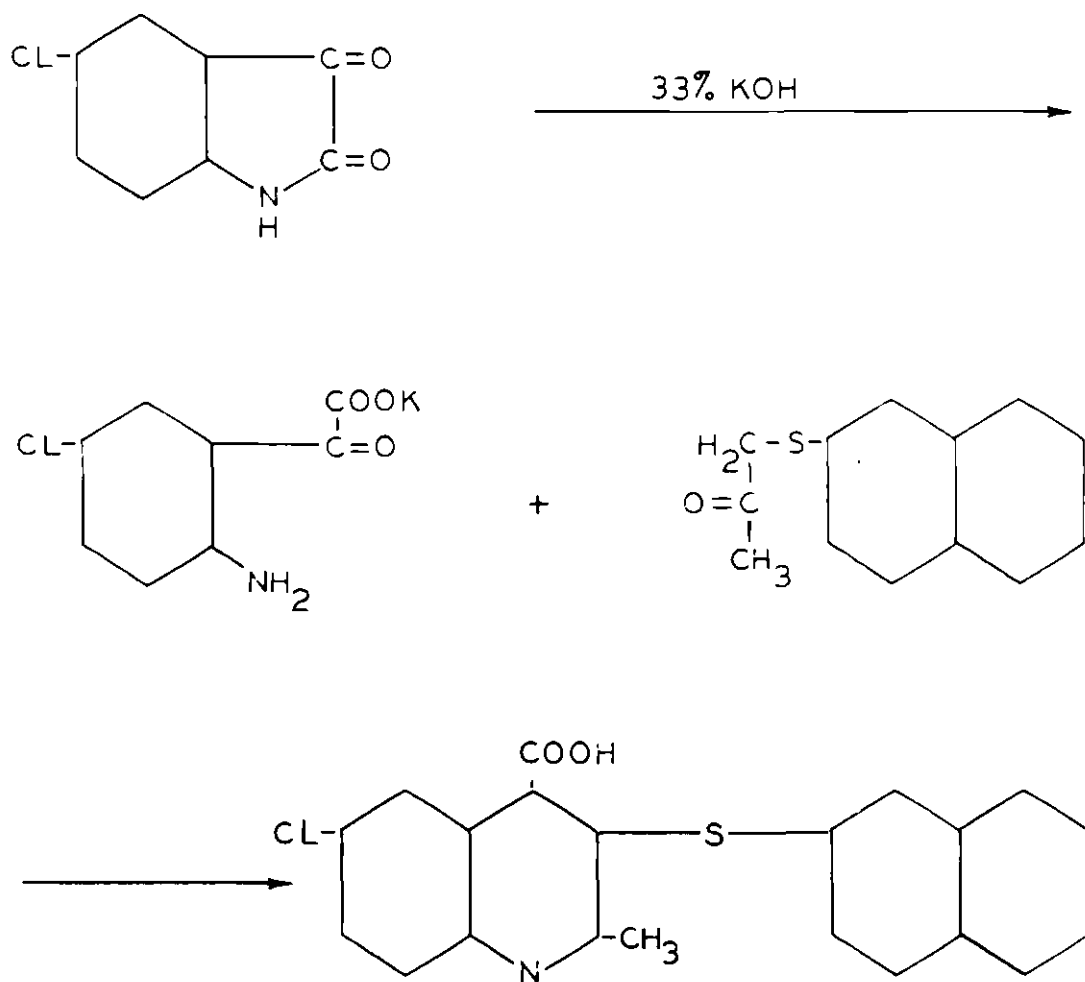
THE PREPARATION OF 5 - CHLOROISATIN [V]



[V]

FIGURE 6

THE PREPARATION OF 6-CHLORO-3-[B-NAPHTHYLMERCAPTO]-4-
QUINALDINECARBOXYLIC ACID [VI]



[VI]

FIGURE 7

THE PREPARATION OF 6-BROMO-3-[B-NAPHTHYLMERCAPTO]-4-
QUINALDINECARBOXYLIC ACID [VII]

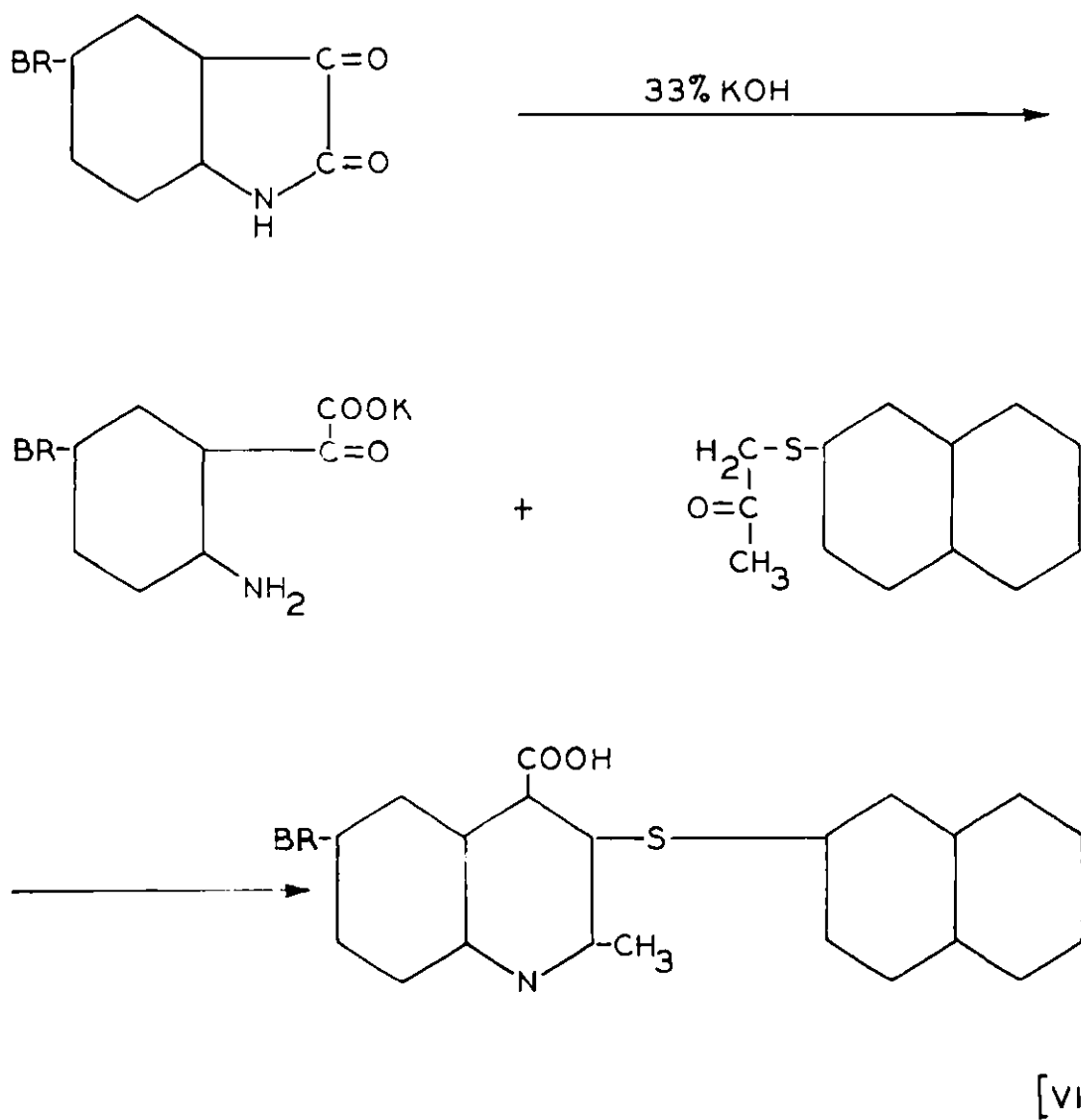


FIGURE 8

THE PREPARATION OF 6-CHLORO-3-[O-TOLYMERCAPTO]-4-QUINALDINECARBOXYLIC ACID [VIII]

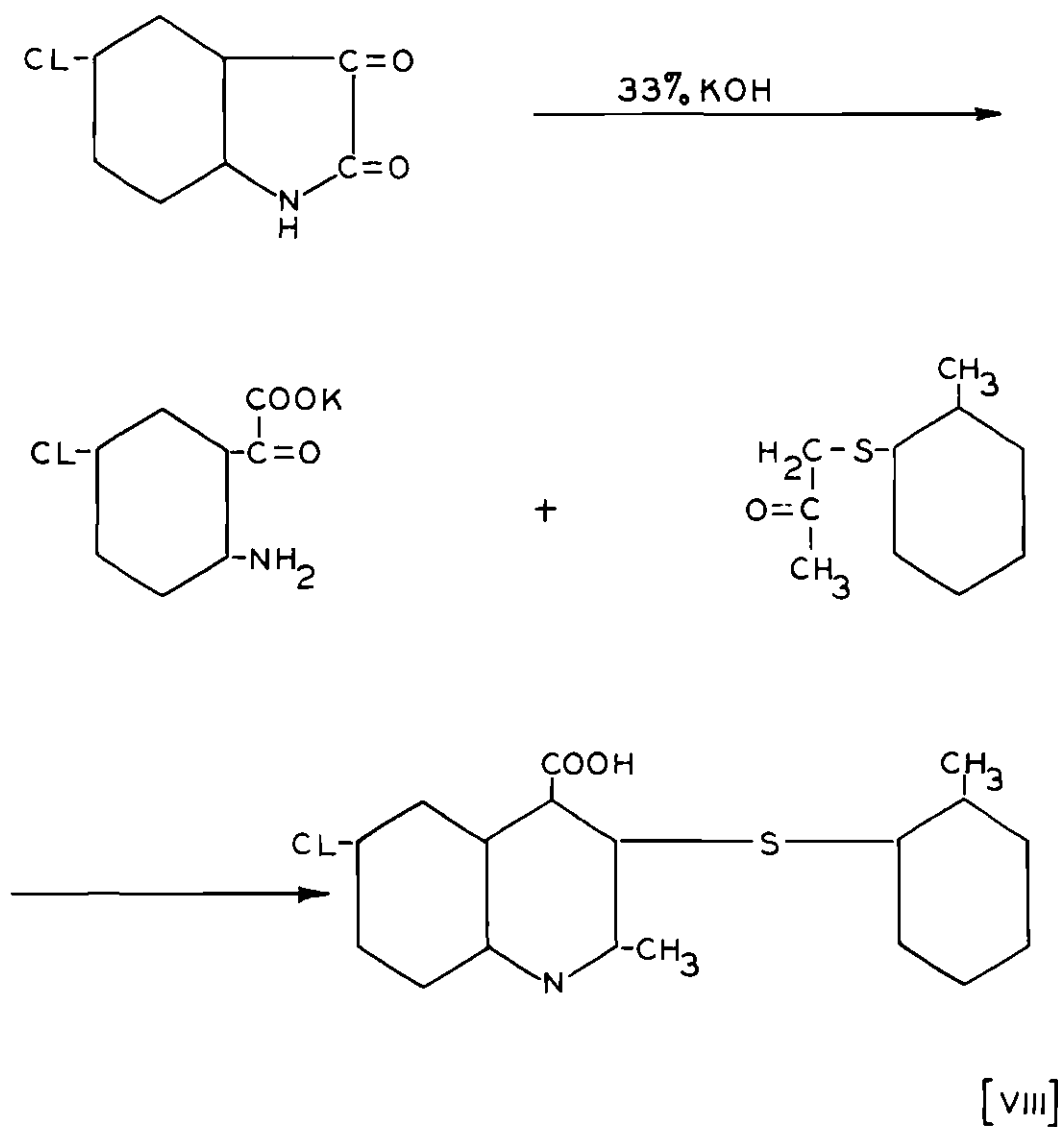
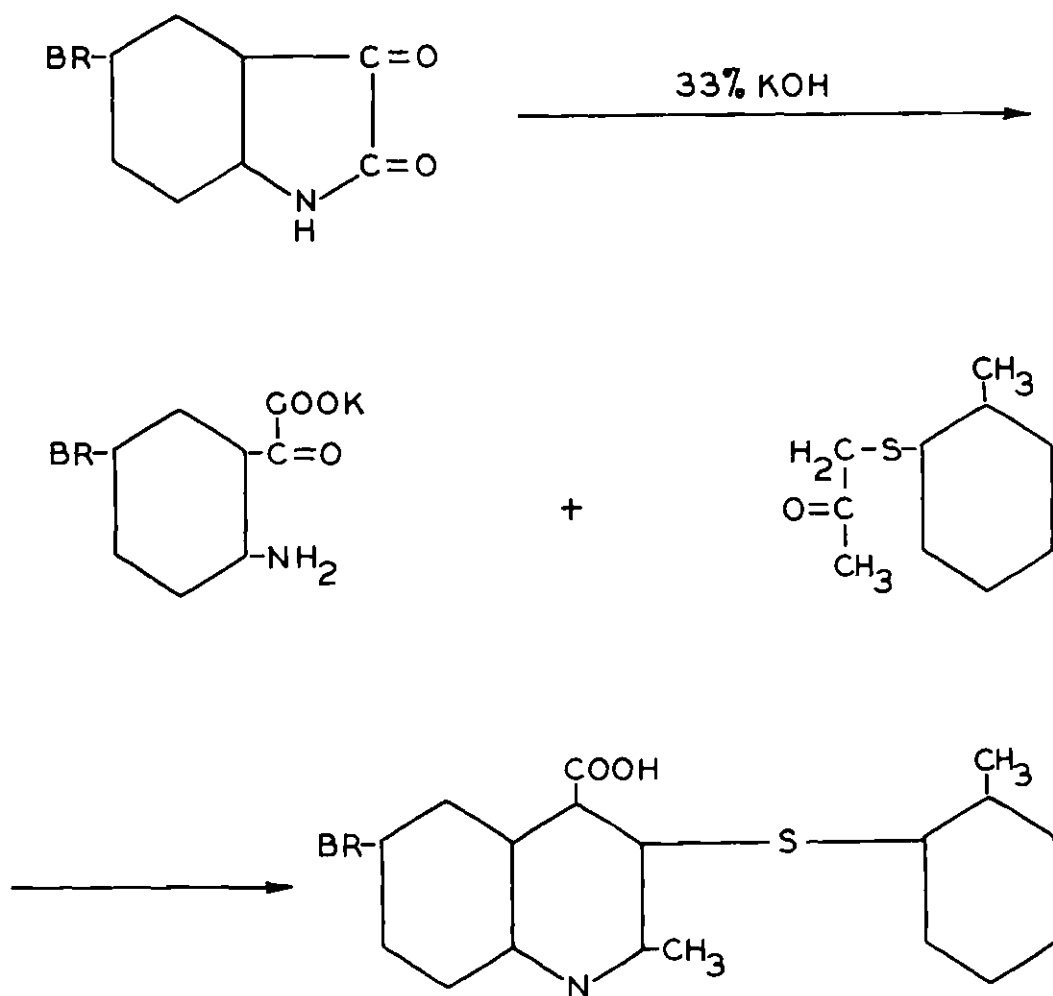


FIGURE 9

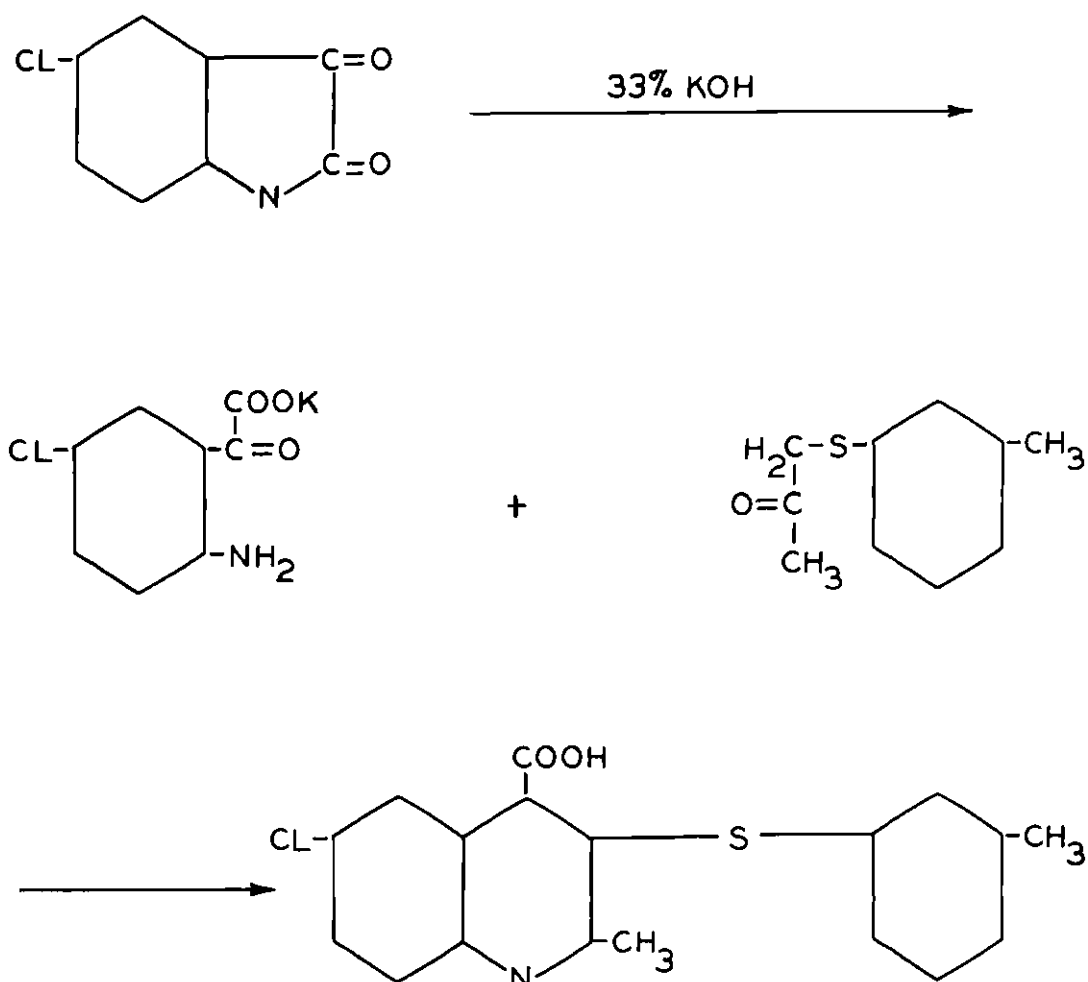
THE PREPARATION OF 6-BROMO-3-[O-TOLYLMERCAPTO]-4-
QUINALDINECARBOXYLIC ACID [IX]



[IX]

FIGURE 10

THE PREPARATION OF 6-CHLORO-3-[M-TOLYLMERCAPTO]-4-QUINALDINECARBOXYLIC ACID [X]



[X]

FIGURE II

THE PREPARATION OF 6-BROMO-3-[M-TOLYLMERCAPTO]-4-QUINALDINECARBOXYLIC ACID [XI]

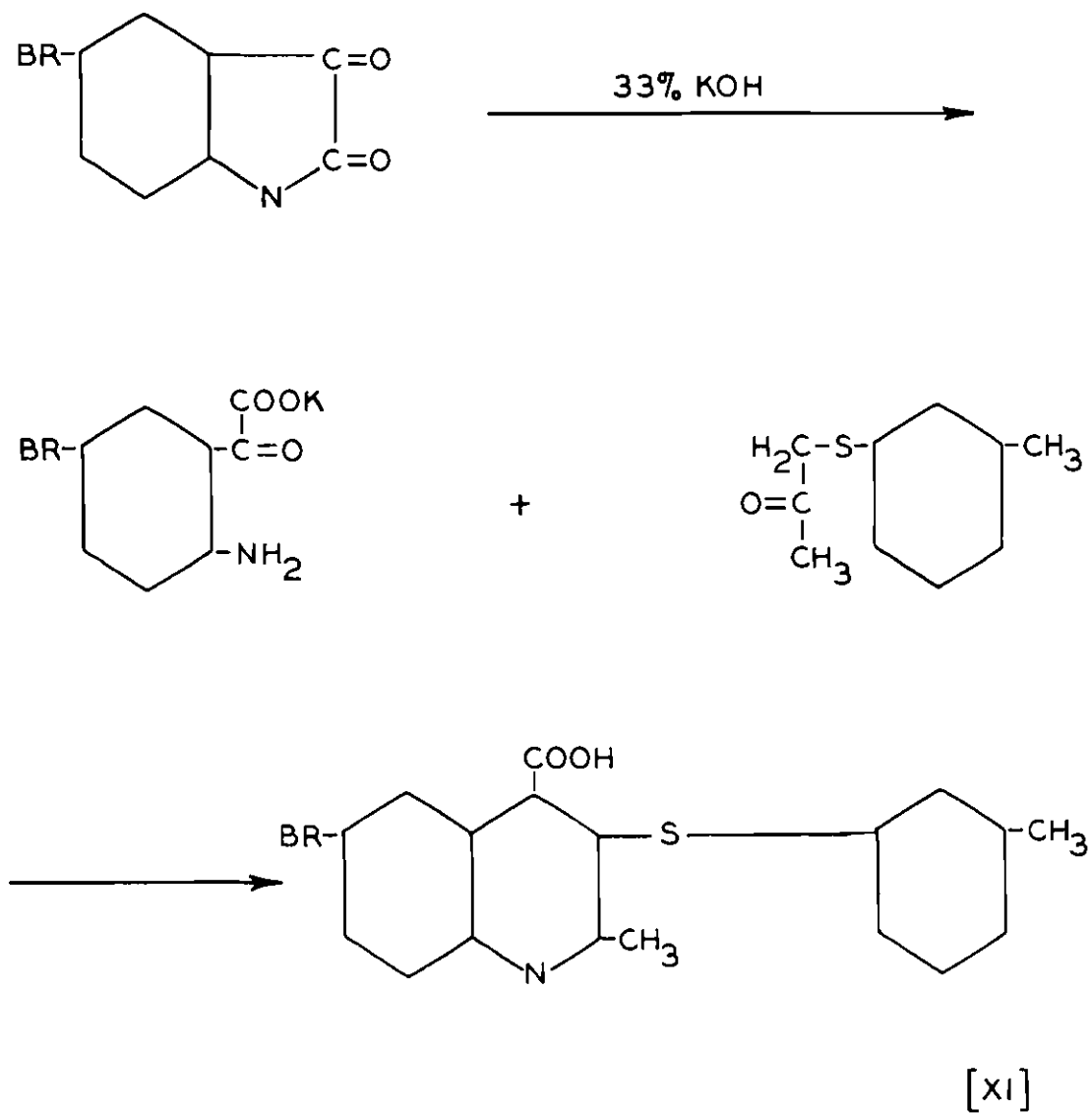


FIGURE 12

THE PREPARATION OF 6-CHLORO-3-[P-TOLYLMERCAPTO]-4-
QUINALDINECARBOXYLIC ACID [XII]

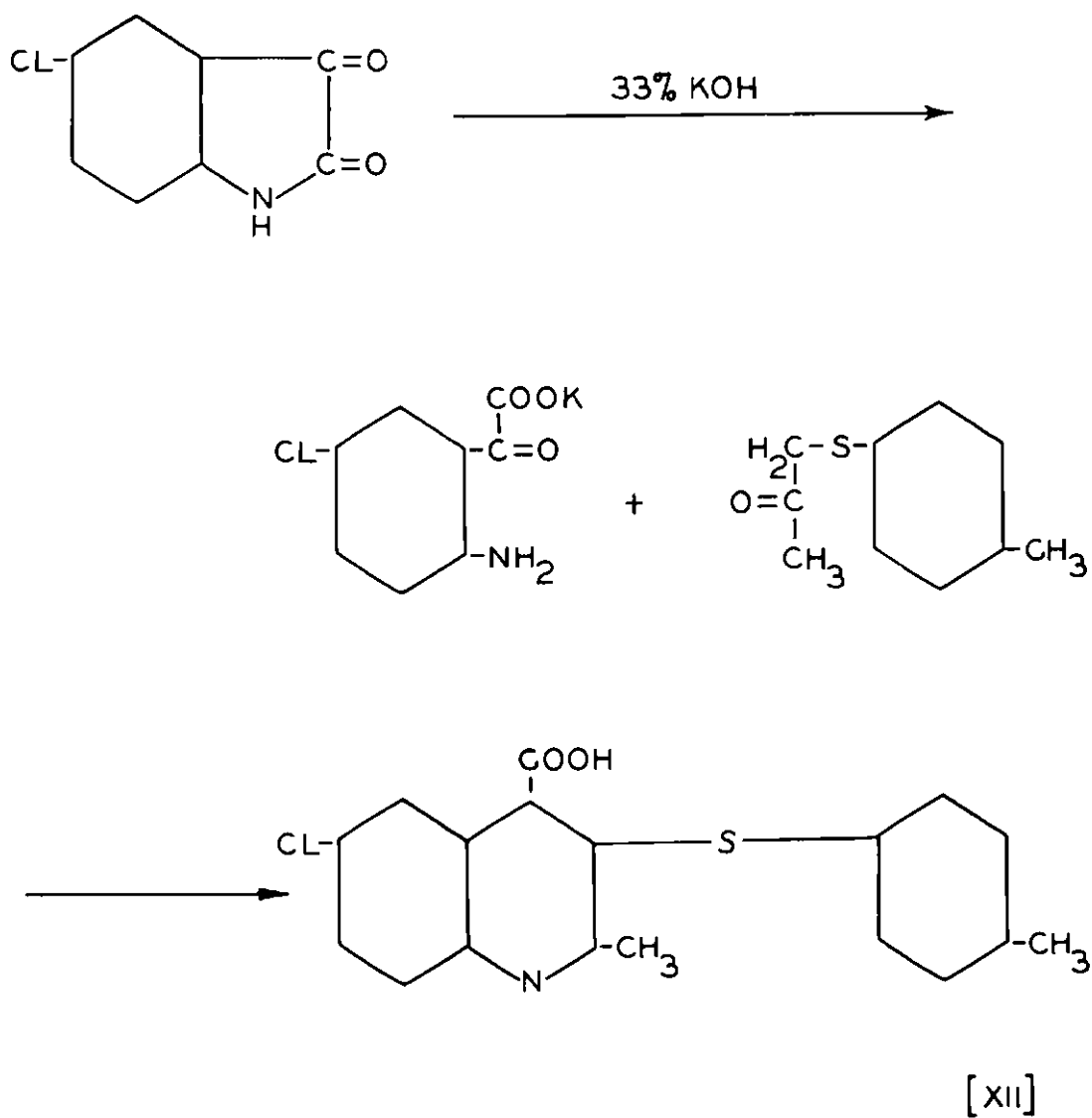
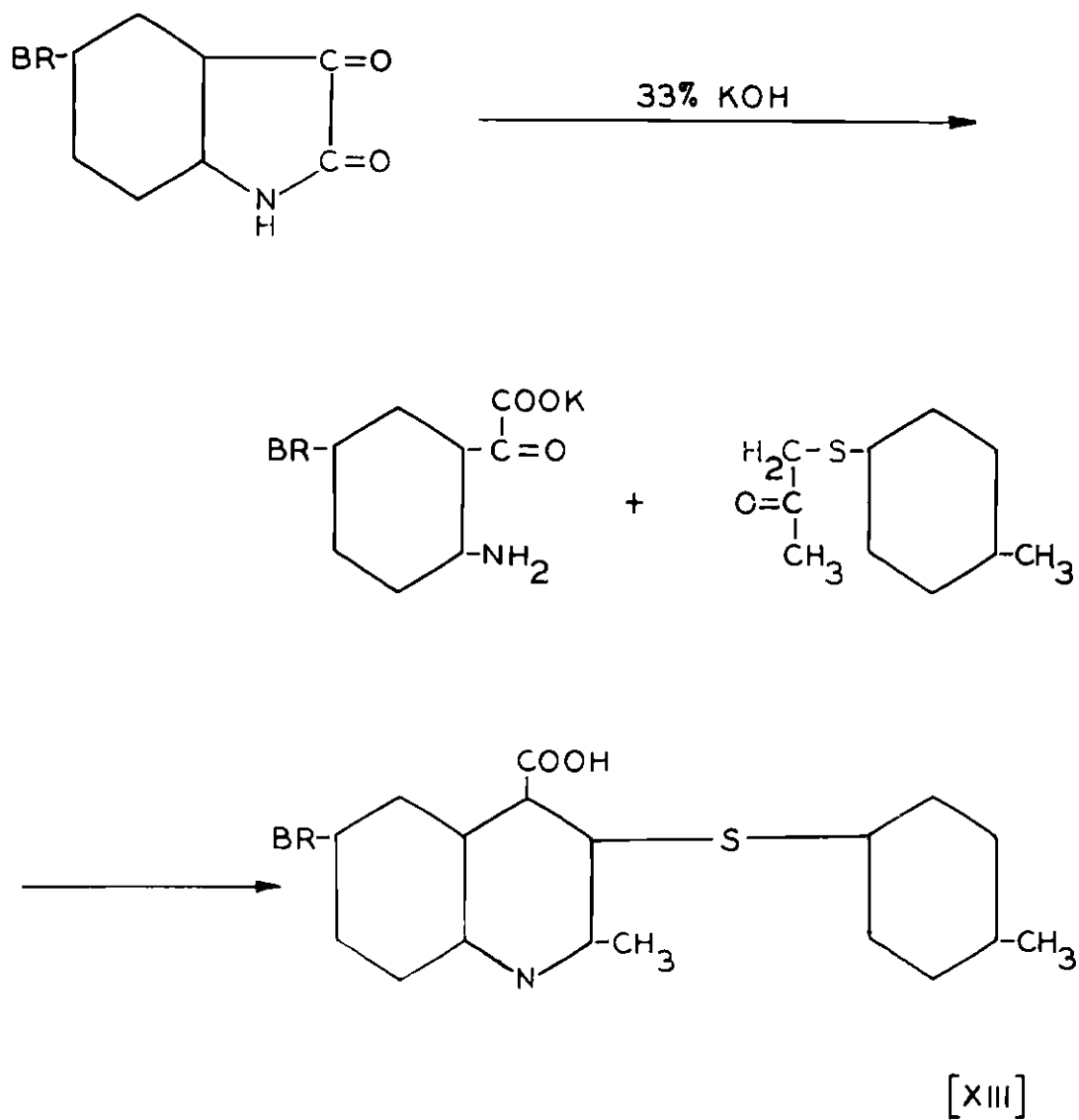


FIGURE 13

THE PREPARATION OF 6-BROMO-3-[P-TOLYLMERCAPTO]-4-
QUINALDINECARBOXYLIC ACID [XIII]



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