8-Sulfonamidoquinolines as a New Class of Organic Reagents

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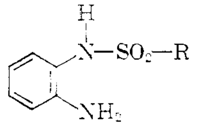
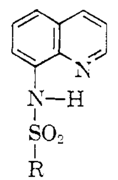
▶ Four sulfonamide derivatives of 8-aminoquinoline were synthesized and put through a qualitative screening process employing a large number of metal ions. Highly colored insoluble chelates were formed with only six metal ions: Ag^+, Hg^{+2}, Cu^{+2}, Pb^{+2}, Co^{+2}, and Zn^{+2}. To obtain a high degree of selectivity or perhaps even specificity, a series of compounds was prepared which would donate only nitrogen atoms to the metal in the event chelation occurred. The acidic function in these reagents is the sulfonamido group (SO_2-NH), while the coordinating species is a basic nitrogen atom. Two classes of compounds were chosen to be synthesized, and the general structures are:



I



II

Studies involving the *p*-toluene derivative of I have been reported (*1*). This paper deals only with some preliminary investigations involving several derivatives of II. The analytical applications of 8-sulfonamidoquinoline derivatives have not been previously investigated. Since the acid strength of the sulfonamido group is about the same as a phenolic hydroxyl group, it is hoped that these derivatives might prove as useful as 8-quinolinol or the sulfur analog, 8-mercaptoquinoline, in metal analysis.

EXPERIMENTAL SYNTHESIS

8 - (*p* - Toluenesulfonamido)quinoline. 8-Aminoquinoline, 4.3 grams (0.03 mole) is placed in a 100-ml. three-necked flask and dissolved in 50 ml. of pyridine. The flask is fitted with a motor stirrer and immersed in an ice water bath. Five and seven-tenths grams (0.03 mole) of *p*-toluenesulfonyl chloride is added in small portions over 2 hours with the solution being stirred throughout. The reaction mixture is then poured into 200 ml. of cold water with vigorous stirring. A pink solid separates out and is filtered and washed thoroughly with water. This solid is then recrystallized from 95% ethyl alcohol, and a white crystalline substance is obtained.

CATION PRECIPITATION TESTS

Composition of Buffer Solutions. Solution *A*. Prepared from 250 ml. of 2*N* acetic acid, 225 grams of sodium acetate (trihydrate), and 500 ml. of distilled water (pH = 5.2).

Solution *B*. Prepared from 40 ml. of 2*N* ammonium hydroxide, 320 grams of ammonium acetate, 30 grams of sodium potassium tartrate, and 850 ml. of distilled water (pH = 8.4).

Solution *C*. Prepared from 500 ml. of 2*N* sodium hydroxide, 275 grams of potassium tartrate, and 500 ml. of distilled water.

Metal Solutions for Precipitation Studies. One tenth molar solutions of the ions below were prepared and employed in the screening process: Li, Na, K, NH_4, Tl, Rb, Ag, Cs, Hg (univalent); Cu, Be, Mg, Ca, Zn, Sr, Su, Pb, Fe, Co, Ni, Cd, Ba, Mn, Pd (bivalent); Al, Sc, Sb, La, Ce, Bi, Fe, Au, Cr, Ru, In, Ga, V (trivalent); Ti, Sn, Zr, Th, Pt (quadrivalent); Sb (quinquevalent).

The nitrate salts were employed where available; in other cases, the chlorides were used. Appropriate amounts of nitric acid were necessary to obtain dissolution of the nitrates of Be, Zr, Bi, Hg^+, and Hg^{+2}. Hydrochloric acid was necessary to dissolve the chlorides of Ti, Sn^{+2}, Sn^{+4}, V, Sb, Pt, and Au.

Preparation of Organic Reagent Test Solutions. Reagent solutions, 0.1*M*, were prepared by dissolving an appropriate amount of reagent in either 95% ethyl alcohol or acetone.

Testing Procedure. One milliliter of metal solution is placed in each of three test tubes to which are added 2 ml. of buffer solution (*A*, *B*, *C*) and 1 ml. of organic reagent solution. Three additional test tubes containing 1 ml. of the organic reagent solution but no metal ions served to determine the behavior of the reagent, while additional control tubes containing 1 ml. of metal solution, 2 ml. of buffer solution, and 1 ml. of water, but no organic reagent, ensured that the possible precipitation of metal as hydroxide or basic salt under the testing conditions could not be mistaken for complex formation. Each test tube was then heated for 15 minutes at 80° C. in a water bath and examined, when cold, for precipitation. This sequence was then repeated with buffer solutions *A*, *B*, and *C* for each organic reagent and metal ion to be studied.

RESULTS

In a few cases, the reagent was insoluble in the cold buffer solution although completely soluble at 80° C., while the metal complex was sufficiently insoluble for its formation to be detected with certainty when observations were made of the hot solution. In some cases where the reagent was insoluble in a particular buffer, both hot and cold, the color or appearance of the metal complex was often sufficiently distinctive to enable its formation to be detected despite the presence of excess reagent.

The results of this extensive investigation are listed below (Table II). Only the positive results are tabulated, and chelate formation was detected in all three buffer media. The remaining ions simply yield clear solutions or insoluble hydroxides. By using controls, as in the testing procedure, hydroxide formation is easily detected.

DISCUSSION

The 8-sulfonamidoquinolines investigated are much more selective than both the related 8-quinolinol and 8-mercaptoquinoline. The six metal ions chelated in each instance are Ag^+, Cu^{+2}, Zn^{+2}, Pb^{+2}, Co^{+2}, and Hg^{+2}.

The chelates differ greatly from those of 8-quinolinol and 8-mercaptoquinoline in their solubility. They do not dissolve in the common nonpolar organic solvents or in the polar ones such as dimethylformamide, pyridine, and nitromethane.

On the basis of elemental analysis and infrared studies, structures have been assigned to the chelates. For the 8-

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Table I. Values for the 8-Sulfonamidoquinoline Reagents

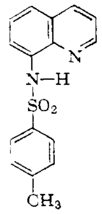
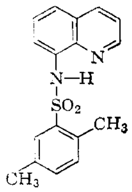
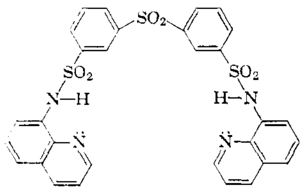
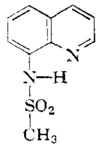
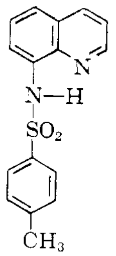
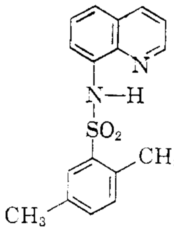
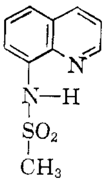
Reagent	Per Cent Yield	M.P. ° C. (Uncorr.)	Per Cent N Calcd.	Per Cent N Found	Per Cent S Calcd.	Per Cent S Found
	76.4	153–154	9.41	9.43	10.72	10.59
	76.5	148–149	8.98	9.00	10.26	10.27
	50	203–204	8.89	8.98	15.24	15.26
	69	143–144	12.61	12.85	14.40	14.32

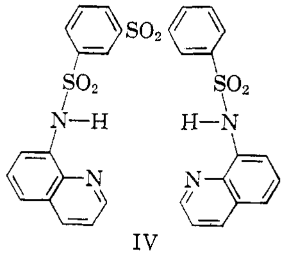
Table II. Results of Cation Precipitation Tests

Ligand


I

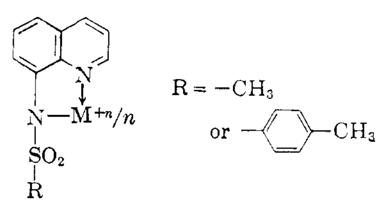

II


III


IV

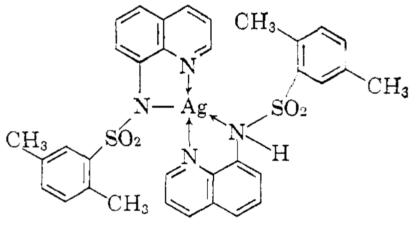
Metal	Color of Chelate I	II	III	IV
Co^{+2}	Pink	Red	Bright red	Red
Hg^{+2}	Green-yellow	Pale yellow	Bright yellow	Pale yellow
Cu^{+2}	Brown	Brown-black	Dark brown	Black
Pb^{+2}	Bright yellow	Bright yellow	Bright yellow	Bright yellow
Zn^{+2}	Green-yellow	Pale yellow	Bright yellow	Pale yellow
Ag^{+}	White	Bright yellow	White	Pale yellow

methanesulfonamidoquinoline and 8-*p*-toluenesulfonamidoquinoline series, the structures are those which can be predicted from a simple consideration of coordination number. The sharp intense band in the 3.1-micron region, characteristic of the N—H stretching frequency, is noticeably absent in the spectra of these chelates.



$M = Co^{+2}, Hg^{+2}, Pb^{+2}, Cu^{+2}, Zn^{+2}, Ag^{+}$

The same holds true for all the chelates of 8-(2,5-dimethylbenzenesulfonamido)-quinoline except the one for silver. The structure assigned is shown below, and elemental analysis yielded the following: $N_{calc.}$ 7.67, N_{found} 7.87%; $S_{calc.}$ 8.75, S_{found} 8.72%.



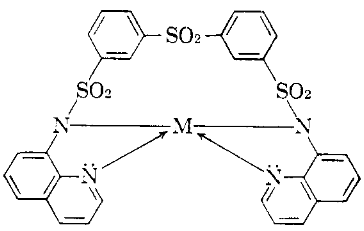
The chelate melts with decomposition at about 160° C., whereas most of the chelates in this study fail to melt at temperatures up to 300° C. In addition, the infrared spectrum shows a sharp band in the 3-micron region attributable to the presence of N—H in the chelate.

An analogous situation was sought and found for the silver chelate of 8-quinolinol. Block, Bailar, and Pearce (*2*) concluded that the yellow complex is a univalent silver compound namely $AgC_9H_6ON.C_9H_7ON$. Hein and Regler (*4*) report the formation of a white precipitate upon the addition of 8-quinolinol to a solution of silver nitrate. This material, on recrystallization from aqueous ammonia, gave a yellow material. From the analysis of these materials, the authors suggest that the white material may have the composition $[Ag(C_9H_6NOH)_2]NO_3$, and the yellow material obtained from ammoniacal solutions on recrystallization, $AgC_9H_6ON.C_9H_7ON$. The silver complex of 8-(2,5-dimethylbenzenesulfonamido)-quinoline is yellow while the 1 to 1 chelates of the previous two ligands discussed are white.

Other instances where this extra mole of ligand shows up may be found in several of the complexes of 8-mercaptoquinoline (*5*). The complex formed by precipitation of silver in acid medium is believed to have the composition $C_9H_6NSAg.C_9H_6NSH.3H_2O$.

It is difficult to understand the nature of the bonding between the normal chelate and the extra ligand molecule. It has been suggested that the extra molecule is bound merely by weak lattice forces.

The metal chelates of 3,3′-bis(quinoline-8-sulfamoyl) biphenyl sulfone are formulated as fused ring systems consisting of two 5-membered rings and one 12-membered ring. It was hoped that combining such a bis(bidentate) ligand with a tetracoordinate metal ion would lead to a linear polymer. However, due to the flexibility of the biphenyl sulfone system, the four sites can assume close proximity and chelate one mole of metal leading to the formation of the structure shown here:

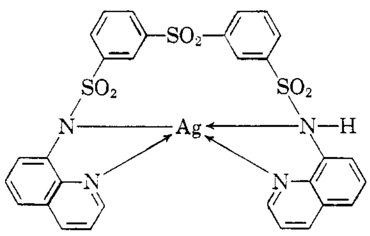


It is evident that the proposed structures of complexes with chelate rings containing more than six atoms are not firmly established. Lack of x-ray and other conclusive data, the several possible linkages, and the possibility of polymerization, all tend to make the proposed structures highly speculative.

Several examples of condensed ring chelates containing a large membered ring are found in the literature (*3, 6, 7*).

In the chelates of 3,3′-bis(quinoline-8-sulfamoyl) biphenyl sulfone, the stability of the smaller rings and the flexibility of the biphenyl sulfone system probably account for the formation of these complexes.

The structure assigned to the yellow silver chelate is:



Elemental analysis checks for a 1 to 1 mole ratio of ligand to metal atom and the infrared spectrum shows a sharp band in the 3-micron region attributable to the presence of N—H in the chelate.

The nature of the yellow compound formed in the reaction between lead and 3,3′-bis(quinoline-8-sulfamoyl) biphenyl sulfone is in doubt. The results of two analyses run on separate samples check fairly well but are about one half the calculated values. Two possibilities are polymer formation or a complex with an unusually large metal to ligand ratio.

Further work will include the development of quantitative applications and a study of the possibilities of further specificity within the six metal ions. With the proper choice of one or more masking agents, it is hoped that high specificity will be obtained.

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New Fluorometric Micromethod for the Determination of Reserpine

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▶ A new, rapid, highly sensitive, and reproducible micromethod for the fluorometric determination of reserpine has been developed. Concentrations of reserpine as low as 0.005 μg. per milliliter can be measured. The method does not measure the oxidative breakdown products of reserpine which occur frequently in pharmaceutical formulations. A solution of reserpine in glacial acetic acid is heated with a 1% solution of p-toluenesulfonic acid in glacial acetic acid for 10 minutes, and the resulting fluorescence is measured.

Because it is an important therapeutic agent, many analytical procedures have been developed for the quantitative determination of reserpine. All of these procedures include many steps of quantitative separation such as: extraction, paper and column chromatography, paper ionophoresis, etc.

Several methods are based upon the ultraviolet absorption properties of reserpine; among them is that of Sakal and Merrill (*13*) which combines the ultraviolet absorption method with paper ionophoresis. Banes (*1*) employs chromatography to isolate reserpine. McMullen *et al.* (*11*) remove the decomposition products of reserpine by an extraction with dilute hydrochloric acid and sodium bicarbonate solutions.

In the same paper the authors give a procedure for the fluorometric determination of reserpine by heating with a mixture of sulfuric, hydrochloric, and acetic acids. This method is about 20 times less sensitive than the method described here. Poet and Kelly (*12*) determine reserpine fluorometrically by heating a sulfuric acid solution of reserpine in the presence of selenious acid. The sensitivity of this method appears