[Chem. Pharm. Bull. 13(1) 33 ~ 39 (1965)]

UDC 543-4 : 615.778.25

6. **Satoshi Mizukami and Masao Kono :** Studies on Sulfonamide Derivatives as Analytical Reagent. I. 2′-Mercapto-sulfonanilide Derivatives.

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Since the acid strength of sulfonamido group is approximately the same as that of phenolic hydroxyl group, it might be expected that some of the compounds carrying sulfonamido group would be useful as the reagent in metal analysis. Only a few reports dealing with the analytical application of the compounds carrying sulfonamido group has been found,[1~4] and in addition, the compounds containing both sulfonamido- and sulfur containing groups in the molecule as the donor groups have not been investigated as the analytical reagents. From the above mentioned point of view, a series of the compounds containing both sulfonamido- and sulfur containing groups as the functional group were studied, in an attempt to find the useful organic reagents. This paper deals with the syntheses of a series of sulfonamide derivatives of 2-aminobenzenethiol, 2′-mercapto-sulfonanilide (I), and also the investigations of their properties as the analytical reagents.

Synthesis of Reagent

A procedure of the synthesis of I is shown in Chart 1. The disulfide (Ⅲ) was prepared by reacting 2,2′-dithiodianiline (Ⅱ) with alkane- or arene-sulfonyl chloride in pyridine, and Ⅲ was reduced with sodium sulfide to give the sodium salt of I (Ⅳ). The compounds obtained are listed in Tables I and Ⅱ. As Ⅳ reacted with methyl iodide to give N-methyl-2′-methylthio-sulfonanilide (Ⅴ), Ⅳ was confirmed to be the disodium salt of I. This compound was stable at room temperature in atmosphere and contains a few moles of water or ethanol as solvent of crystallization. The compound (Ⅳ) could be converted into I on treating with acid, but it was found to turn easily into the disulfide (Ⅲ) by air. As I could not be isolated, Ⅳ was used for the following investigation of the analytical application.

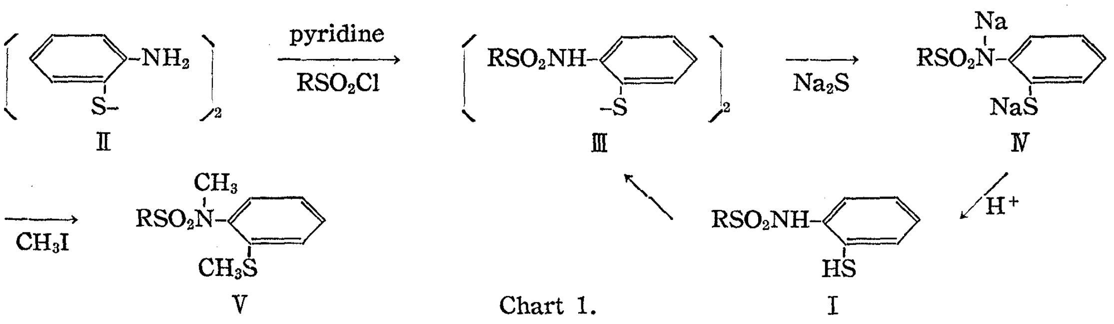

Chart 1.

Test of Color Reaction with Metal Ions

A number of qualitative tests were carried out to investigate the color reaction with the common metal ions. The reagent (Ⅳ) reacted respectively with aluminium (III),

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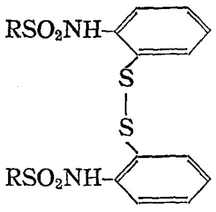
1) G. Schetty, H. Ackermann : Angew. Chem., **70**, 222 (1958).

2) J. H. Billman, N. S. Janetos, R. Chernin : Anal. Chem., **32**, 1342 (1960).

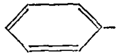
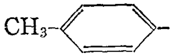
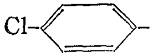
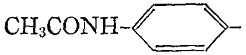
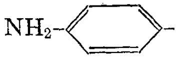
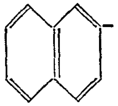
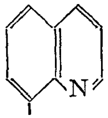
3) J. H. Billman, R. Chernin : *Ibid.*, **34**, 408 (1962); *Ibid.*, **36**, 552 (1964).

4) T. R. Williams, F. G. Burton : Anal. Chim. Acta, **27**, 351 (1962).

Table I.

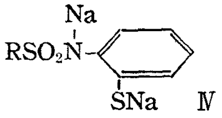


III

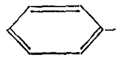
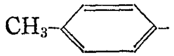
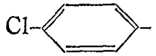
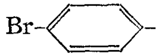
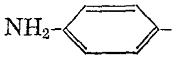
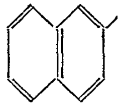
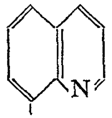
No.	R	Yield (%)	m.p. (°C)	Recryst. solvent	Formula	Analysis (%)							
						Calcd.				Found			
						C	H	N	S	C	H	N	S
IIIa	CH$_3$	51	142.5	C$_2$H$_5$OH	$C_{14}H_{16}O_4N_2S_4$	41.56	3.99	6.92	31.70	41.79	4.04	7.06	31.63
IIIb	C$_2$H$_5$	49	109	C$_2$H$_5$OH	$C_{16}H_{20}O_4N_2S_4$	44.42	4.66	6.48	29.64	44.55	4.74	6.62	29.37
IIIc		63	150	C$_2$H$_5$OH	$C_{24}H_{20}O_4N_2S_4$	54.52	3.81	5.30	24.26	54.82	3.93	5.29	24.02
IIId		69	162	C$_2$H$_5$OH	$C_{26}H_{24}O_4N_2S_4$	56.09	4.35	5.03	23.04	56.32	4.56	5.16	23.30
IIIe		60	148	C$_2$H$_5$OH	$C_{24}H_{18}O_4N_2Cl_2S_4$	48.24	3.04	4.69	21.46	48.16	3.18	4.93	20.73
IIIf		59	157.5	C$_2$H$_5$OH	$C_{24}H_{18}O_4N_2Br_2S_4$	41.99	2.64	4.08	18.68	42.15	2.81	4.06	18.61
IIIg		67	220	CH$_3$COOC$_2$H$_5$ C$_2$H$_5$OH	$C_{28}H_{26}O_6N_4S_4 \cdot 2C_2H_5OH$	52.30	5.21	7.62	17.54	52.54	5.46	7.54	17.39
IIIh[a]		48	215.5	dioxane C$_2$H$_5$OH	$C_{24}H_{22}O_4N_4S_4$	51.59	3.97	10.03	22.96	51.76	4.21	9.91	22.66
IIIi		72	173	CH$_3$COOC$_2$H$_5$ C$_2$H$_5$OH	$C_{32}H_{24}O_4N_2S_4$	61.12	3.84	4.46	20.39	61.33	3.93	4.50	20.47
IIIj		64	255~256	dioxane C$_2$H$_5$OH	$C_{30}H_{22}O_4N_4S_4$	57.12	3.52	8.88	20.33	56.87	3.51	8.74	19.99

a) IIIh was prepared by hydrolysis of IIIg with 10% sodium hydroxide.

Table II.



IV

No.	R	Yield (%)	m.p. (°C)	Recryst. solvent	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Calcd. Na	Found C	Found H	Found N	Found Na
IVa	CH_3	26	—	H_2O	$C_7H_7O_2NS_2Na_2 \cdot 3H_2O$	27.90	4.34	4.64	15.18	27.71	4.56	4.35	15.09
IVb	C_2H_5	29	—	80% C_2H_5OH	$C_8H_9O_2NS_2Na_2 \cdot \frac{1}{2}C_2H_5OH \cdot H_2O$	41.76	4.67	4.63	15.20	36.04	4.95	4.67	14.92
IVc		32	—	H_2O	$C_{12}H_9O_2NS_2Na_2 \cdot 2H_2O$	41.73	3.79	4.05	13.31	41.62	3.90	4.02	13.35
IVd		34	—	H_2O	$C_{13}H_{11}O_2NS_2Na_2 \cdot 4H_2O$	39.49	4.84	3.45	11.62	39.58	4.85	3.52	11.35
IVe		45	—	H_2O	$C_{12}H_8O_2NS_2ClNa_2 \cdot 3H_2O$	36.23	3.54	3.52	11.55	36.07	3.73	3.27	11.49
IVf		37	—	H_2O	$C_{12}H_8O_2NS_2BrNa_2 \cdot 4H_2O$	31.31	3.50	3.04	9.34	31.12	3.55	2.89	9.28
IVh		34	—	60% C_2H_5OH	$C_{12}H_{10}O_2N_2S_2Na_2 \cdot 4H_2O$	36.36	4.58	7.07	11.60	36.45	4.71	7.19	11.30
IVi		42	—	H_2O	$C_{16}H_{11}O_2NS_2Na_2 \cdot 3H_2O$	46.48	4.14	3.38	11.12	46.72	3.91	3.14	10.40
IVj		39	253	H_2O	$C_{15}H_{10}O_2N_2S_2Na_2 \cdot 4H_2O$	41.76	4.21	6.49	10.65	41.71	4.13	6.57	10.61

titanium (iii), vanadium (v) monoxide, chromium (ii), iron (iii), cobalt (ii), nickel (ii), copper (ii), zinc (ii), palladium (ii), silver (i), cadmium (ii), tin (iv), barium (ii), mercury (ii), lead (ii), and dioxouranium (vi) to produce a precipitate in neutral and alkaline medium, but not in acid medium. Among the above mentioned ions only eight metal ions, such as iron (iii), cobalt (ii), nickel (ii), copper (ii), palladium (ii), silver (i), mercury (ii), and lead (ii), produced the colored precipitates. These results are shown in Table III. In the case of iron (iii), the color of the precipitate faded after a few minutes, and this is considered to be due to the oxidation and reduction which take place between the mercapto group and iron (iii). In the case of cobalt (ii), nickel (ii), and copper (ii), it was found that the colored products dissolved in water; not precipitated in the presence of excess reagent but precipitated in the presence of excess metal ions. It seems likely that the products are water-soluble complex, since the products were soluble in organic solvents as well as in water, and not decomposed in strong alkaline medium. Among the three metal ions, cobalt (ii) produced most stable complex and it was soluble in water most easily.

Table III. Color Reaction of Metal Ions with IV[a]

Compd. / Metal ion	IVa	IVb	IVc	IVd	IVe	IVf	IVh	IVi	IVj
Fe (iii)	V	V	V	V	V	V	V	V	V
Ni (ii)	(B)	(B)	VB(OB)	VB(OB)	BV(BV)	BV(BV)	B(B)	BV(VB)	OB
Co (ii)	(G)	(G)	GB(G)	GB(G)	GB(G)	GB(G)	GB(G)	GB(G)	BlG(BlG)
Cu (ii)	(V)	(V)	BlG(V)	BlB(V)	BlB(V)	BlB(V)	BlB(V)	BlB(V)	BlB(V)
Pd (ii)	O	O	OR	O	OB	OB	O	O	RO
Ag (i)	Y	Y	Y	Y	Y	Y	Y	Y	O
Pb (ii)	Y	Y	Y	Y	Y	Y	Y	Y	Y
Hg (ii)	Y	Y	Y	Y	Y	Y	Y	Y	Y

B: brown, Bl: blue, G: green, O: orange, R: red, V: violet, Y: yellow

a) Symbols in parentheses indicate color of solution, but other symbols indicate color of precipitate.

The limits of identification of cobalt (ii), nickel (ii), copper (ii), and palladium (II) with IV were determined, because the reactions with these metal ions seemed to be sensitive. As seen in Tables IV, IV was found to be a sensitive reagent to copper (ii), nickel (ii), and cobalt (ii). From these results, IV was expected to be useful for qualitatively analysis of cobalt (ii), nickel (ii), and copper (ii).

Table IV. Limit of Identification of Metal Ions (μg. per 0.05 ml.)

Compd. / Metal ion	IVa	IVb	IVc	IVd	IVe	IVf	IVh	IVi	IVj
Ni (ii)	0.5	0.25	0.5	0.5	0.5	0.5	0.5	0.5	1.0
Co (ii)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	1.0
Cu (ii)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.5
Pd (ii)	2	2	2	2	2	2	2	2	2.5

Spectrophotometric Determination of Cobalt with 2′-Mercaptobenzenesulfonanilide Disodium Salt (IVc)

The previous studies were conducted with the hope that the sensitivity of IV for cobalt (ii) could be carried over into a spectrophotometric determination. The reagent employed was 2′-mercaptobenzenesulfonanilide disodium salt (IVc). Color development with complex formation was almost instantaneous and the intensity of the color was found to be constant for eight hours after the reaction. Beer's law is followed over the range tested (50 to 900 μg. per ml.) by measurement of absorbance at 610 mμ.

It may be concluded from the results of this study that these reagents (IV) were useful for identification of cobalt (II), nickel (II), and copper (II), and spectrophotometric determination of cobalt (II).

Experimental

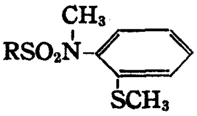
2′,2‴-Dithiobis(sulfonanilide) (III)——To a solution of 0.1 mole of 2,2′-dithiodianiline (II) in dried pyridine (100 ml.) was added slowly 0.2 mole of alkane- or arene-sulfonyl chloride with stirring at 0°. The reaction mixture was allowed to stand at room temperature for 2 days, and ice-water was added with stirring. The precipitate was collected and recrystallized from an organic solvent as shown in Table I to give III.

N^1,$N^{1'}$-(*o*,*o*′-Dithiodiphenyl)bissulfanilamide (IIIh)——Twelve grams of N^1,$N^{1'}$-(*o*,*o*′-dithiodiphenyl)-N^4,$N^{4'}$-diacetylbissulfanilamide (IIIg) was heated with 30 ml. of 10% NaOH for 3 hr. on a water bath. After cooling, the reaction mixture was acidified with AcOH and the precipitate was recrystallized from the solvent as shown in Table I to give IIIh.

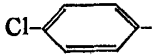
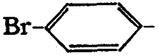
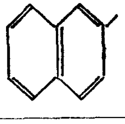
2′-Mercapto-sulfonanilide Disodium Salt (IV)——To 5 ml. of 10% Na_2S was added 0.01 mole of III. The mixture was heated for 5 min. on a water-bath. After cooling at 0°, Na_2S was added to saturation. The mixture was stood at 0°, the precipitate was collected and recrystallized from the solvent as shown in Table II to give IV.

N-Methyl-2′-methylthio-sulfonanilide (V)——To a solution of 0.001 mole of IV in 5 ml. of EtOH was added 0.002 mole of methyl iodide. After heating to reflux on a water bath for 30 min., the solvent was removed under vacuum on a water bath, and water was added to the residue to separate crystals. The crystals were collected and recrystallized from organic solvent as shown in Table V to give V.

TABLE V.



V

R	Yield (%)	m.p. (°C)	Recryst. solvent	Formula	Analysis (%) Calcd. C	H	N	S	Found C	H	N	S
CH_3	41	72.5	$C_2H_5OC_2H_5$	$C_9H_{13}O_2NS_2$	46.72	5.66	6.06	27.72	46.78	5.74	6.29	27.90
	72	123	CH_3OH	$C_{14}H_{15}O_2NS_2$	57.31	5.15	4.77	21.86	57.14	5.19	4.80	21.69
	78	120.5 ~121	CH_3OH	$C_{15}H_{17}O_2NS_2$	58.60	5.57	4.55	20.86	58.30	5.63	4.56	20.79
	67	131.5	CH_3OH	$C_{14}H_{14}O_2NS_2Cl$	51.29	4.30	4.27	—	51.19	4.36	4.31	—
	65	152	C_2H_5OH	$C_{14}H_{14}O_2NS_2Br$	45.16	3.76	3.76	—	45.18	3.92	3.53	—
	73	162	C_2H_5OH	$C_{18}H_{19}O_2NS_2$	62.95	4.98	4.08	18.67	63.11	5.07	3.93	18.35

Color Tests with Metal Ions——The metal salts were dissolved to a concentration of about 1 to 5%, and the solutions were used as metalic test solutions. A drop from each test solution was added to 0.5 ml. of a 1% solution of the reagent (IV).

Determination of Limit of Identification of Metal Ions——After a drop of the aqueous solution of metal ion was treated on a spot plate with a drop of 1% solution of the reagent (IV), the absence or presence of a color product was noted. From above method, the limited concentration of metal ion which could be identified was tested.

Spectrophotometric Determination of Cobalt with 2′-Mercaptobenzenesulfonanilide Disodium Salt (IVc)

1) **Apparatus**——Absorbance measurements were made with a Hitachi Model EPU-2A Spectrophotometer, using 1 cm. glass transmission cells. All experiments were carried out at 23~25°.

2) **Reagents**——Standard cobalt solution : A stock solution containing 1 mg. of cobalt per ml. was prepared by dissolving cobalt acetate crystals of analytical grade in water. This solution was then standardized against a standard EDTA solution.[5] Dilution of this solution was made as required.

2′-Mercaptobenzenesulfonanilide solution : A 1% solution was prepared by dissolving 1 g. of Ⅳc in 100 ml. of buffer solution (pH 10).

Buffer solution : Britton-Robinson's buffer solution.[6]

3) **Determination Method**——To 1 ml. of the sample solution made more alkaline than pH 5 in a 10 ml. volumetric flask, 2 ml. of 2′-mercaptobenzenesulfonanilide solution was added. The solution was allowed to stand for 2 min. at room temperature and then the volume of the content was made up to 10 ml. with buffer solution (pH 10). The absorbance of the solution was measured at 610 mμ using a reagent blank.

4) **Calibration Curve**——Measurements of the absorbance were made with a number of colored solutions containing various amounts of cobalt. Fig. 1 shows that Beer's law is obeyed over the range of 50 to 900 μg. of cobalt.

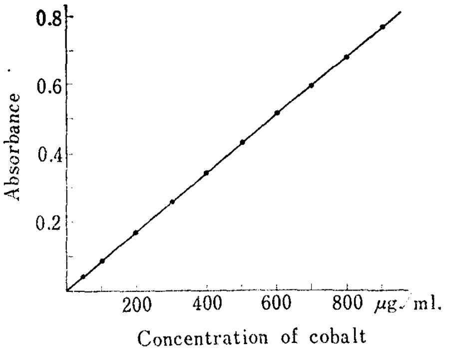


Fig. 1. Calibration Curve of Cobalt

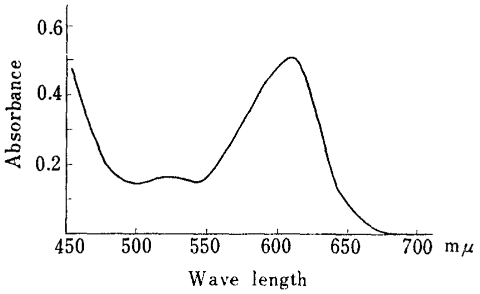


Fig. 2. Absorption Spectrum of Cobalt Complex of Ⅳc

5) **Discussion of Conditions**——The conditions for the assay were examined changing only one factor at a time while keeping other the factors constant, using up to 600 μg. per ml. standard solution of cobalt.

a) Absorption spectrum : Fig. 2 shows the absorption spectrum of solution containing 600 μg. of cobalt. The wave length of the absorption maximum was 610 mμ.

b) pH of colored solution : The absorbances of colored solutions at various pH's were determined. When pH was higher than 8.7, absorbances were constant and the reagent (Ⅳc) precipitated when pH was lower than 8.7.

c) pH of sample solution : As shown in Table Ⅵ, no change in absorbance was observed in the sample solution which was made higher than pH 4.

Table Ⅵ. Effect of pH of Sample Solution upon Absorbance

pH	2.5	3.5	4.0	5.0	6.0	7.0	7.5
Absorbance	0.451	0.499	0.506	0.508	0.504	0.506	0.507

d) Concentration of the reagent (Ⅳc) : After changing the volume of 2′-mercaptobenzenesulfonanilide solution, the absorbances of colored solutions were determined. As shown in Table Ⅶ, full color development required a minimum of 1 ml. of the reagent.

Table Ⅶ. Effect of Concentration of 2′-Mercaptobenzenesulfonanilide upon Absorbance

Reagent soln. (ml.)	0.5	0.7	0.9	1.0	1.2	1.5	2.0	3.0
Absorbance	0.313	0.443	0.502	0.507	0.506	0.504	0.507	0.505

e) Time of the reaction : After changing the time of the reaction, the absorbances of colored solutions were determined, and when the reaction time was more than 1 min., the absorbances were constant.

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5) K. Ueno : "Chelatometric Titration" (in Japanese), 254 (1960). Nankodo, Tokyo.

6) H. T. S. Britton, R. A. Robinson : J. Chem. Soc., **1931**, 1456.

f) Stability of colored solution : After developing the colored solution, it was found that the absorbance was not changed within 8 hr.

The authors are deeply grateful to Dr. K. Takeda, Director of this Laboratory, for his helpful advice and encouragement. They are also grateful to the members of the Elementary Analysis Department for the elementary analysis data.

Summary

2′-Mercaptosulfonanilide derivatives were prepared by the reduction of 2,2′-dithiobissulfonanilide with sodium sulfide and tested as the analytical reagents. These compounds were found to be useful reagents for the identification of copper (II), cobalt (II), and nickel (II), and the spectrophotometric determination of cobalt (II).

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7. **Masao Tomita, Hiroshi Furukawa,**[*1] **Tsang-Hsiung Yang, and Tsung-Jen Lin**[*2] : On the Alkaloids of *Nelumbo nucifera* Gaertn. VIII.[*3] Studies on the Alkaloids of Loti Embryo. (1).[*4] Structure of Isoliensinine, a New Biscoclaurine Type Alkaloid.

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In 1962, Pan Pei-chuan, *et al.*1) reported the isolation of liensinine from Chinese drug "Lien Tze Hsin (蓮子芯)," embryo loti, (embryo of the seed of *Nelumbo nucifera* Gaertn., Fam. Nymphaeaceae) and its structure was shown to be I, based on the result of its Hofmann degradation and permanganate oxidation.[*5]

Recently we isolated a new phenolic tertiary base and a new water-soluble quaternary base from Formosan "Lien Tze Hsin." This paper deals with the structure elucidation of the tertiary base for which we propose the name "isoliensinine."

The free base of isoliensinine resisted all attempts at crystallization. For the preliminary characterization, several crystalline derivatives were prepared. The hydrochloride crystallized from ethanol to yield colorless needles, m.p. 185∼186° and afforded analytical results in agreement with the empirical formula $C_{37}H_{42}O_6N_2 \cdot 2HCl \cdot 4H_2O$. The perchlorate gave prisms from ethanol, m.p. 200∼203°, $[\alpha]_D$ −70.0° (acetone). Analysis afforded results which supported a $C_{37}H_{42}O_6N_2 \cdot 2HClO_4 \cdot H_2O$ formula.

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[*3] Part VII. Z. Kunitomo : Yakugaku Zasshi, **84**, 1100 (1964).

[*4] Preliminary communication of this work appeared in Tetrahedron Letters, No. 37, 2637 (1964).

[*5] The absolute configuration of two asymmetric centers of liensinine (I) had not been determined (cf. *8).

1) Chao Tse-yuan, Chou Yun-lee, Young Pao-tsin, Chou Tsan-quo : Scientia Sinica, **11**, 216 (1962); Pan Pei-chuan, Chou Yun-lee, Sun Tsun-tsi, Kao Yee-sheng : *Ibid.*, **11**, 321 (1962).