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NOVEL METHODS FOR THE PREPARATION OF BENZISOTHIAZOLONES. 2-BENZALAMINOBENZISOTHIAZOLONES

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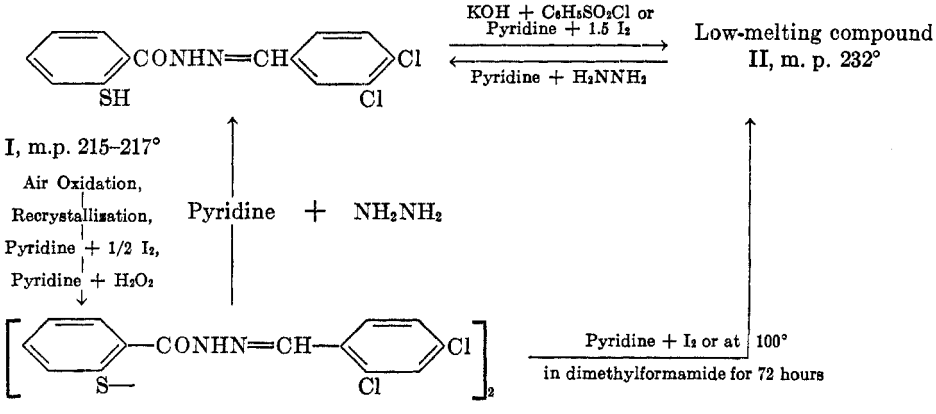
In the course of an investigation directed toward the oxidation of benzalthiosalicylhydrazides (1) to the corresponding disulfides, two products II and III were obtained from I depending on the oxidizing agent employed. It was easily ascertained that III, the high-melting derivative, was a disulfide and initially it was believed that II was another of the three theoretically possible *syn* and *anti* isomers. The salient data concerning the preparation and properties of II and III are contained in Flow Sheet I.

FLOW SHEET I



Compound II could be obtained by oxidation of I with either pyridine and 1.5 moles of iodine or with potassium hydroxide and benzenesulfonyl chloride (2). When pyridine and an equivalent amount of iodine were employed, III was the only isolable entity. III was also prepared by oxidation of I with pyridine and hydrogen peroxide, recrystallization of I from aqueous dimethylformamide, or by air-oxidation of I. The original thiol was regenerated from either II or III by reduction with pyridine and hydrazine hydrate. It was possible to convert III to II by causing a pyridine solution of III to react with a molar amount of iodine or by heating III in dimethylformamide at 100° for 72 hours, albeit that the yield in the latter instance was only 25%.

Inconsistent with the geometrical isomer postulate were the data that (a) the same thiol was regenerated from II or III, (b) a molar rather than a catalytic

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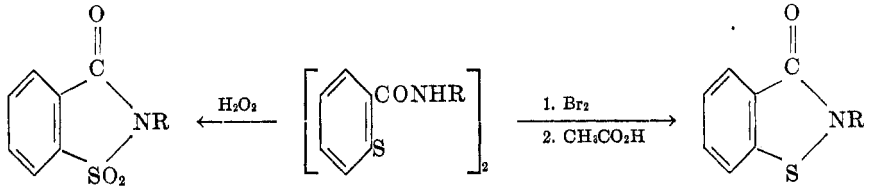
amount of iodine was necessary for conversion of III to II, and (c) careful purification of II and subsequent repeated microanalyses resulted in an empirical formula for II differing from that of III by two less hydrogen atoms. Infrared spectra of II and III were compared and these showed the absence of hydrogen-bonded NH bands in II in the region of 3040–3110 cm^{-1}, whereas III possessed a strong absorption band at 3050 cm^{-1}. Final rejection of the geometric hypothesis occurred when *bis*-(acetone)dithiosalicylhydrazone, a compound incapable of existing in *syn* and *anti* modifications, was caused to react with iodine and the consumption of iodine was observed. This latter experiment which will be referred to later in the text, indicated that some other transformation was occurring.

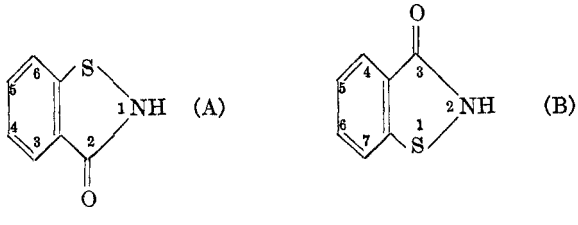
Reissert and Manns (3) described the preparation of a 2-alkylbenzisothiazolone[3] (VI, R = CH_3) from N,N′-dimethyldithiosalicylamide (IV, R = CH_3) by treatment with bromine and acetic acid and McClelland, Warren, and Jackson (4) obtained saccharin derivatives (V, R = CH_3 or C_6H_5) by oxidation of similar amides (IV, R = CH_3 or C_6H_5) with hydrogen peroxide.



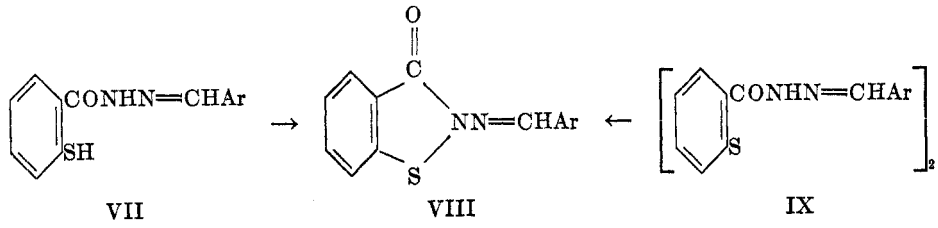
V IV VI

Analogously it was felt that treatment of a benzalthiosalicylhydrazide (VII) dissolved in pyridine with 1.5 moles of iodine or treatment of a *bis*-(benzal)-dithiosalicylhydrazide (IX) with a molar amount of iodine resulted in the production of a 2-benzalaminobenzisothiazolone VIII in accordance with the following equation and that II was a derivative of VIII (Ar = 2,4-dichlorophenyl).

[3] *Ring Numbering.* The earlier workers in the field (4, 5, 11) employed the ring numbering system (A) in which N was 1 and the remainder of the positions were numbered clockwise:



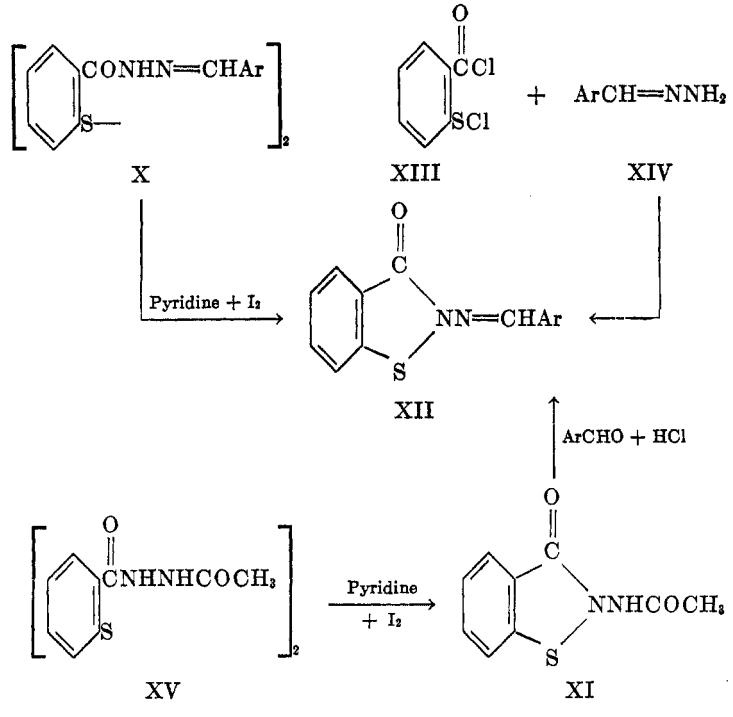
The present authors suggest that the alternative numbering system (B) be employed wherein S is designated as position 1 and numbering occurs counterclockwise. This system has been suggested by the Ring Index, p. 11, No. 736, and it is more rational in the light of the methods by which these compounds are obtained and nomenclature employed in analogous heterocycles such as benzthiazole and benzoxazole.



VII VIII IX

Conclusive corroboration that the benzisothiazolone structure was indeed correct was obtained by comparison of 2-salicylalaminobenzisothiazolone (XII) prepared by oxidation of *bis*-(salicylal)dithiosalicylhydrazide (X) with pyridine and iodine with XII prepared by two different unequivocal methods. These syntheses are outlined in Flow Sheet II.

FLOW SHEET II

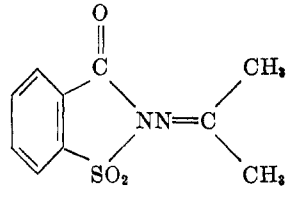


Ar = 2-hydroxyphenyl

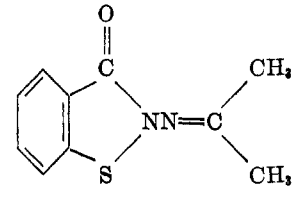
2-Acetylaminobenzisothiazolone (XI) was prepared by the pyridine-iodine oxidation of N,N′-diacetyldithiosalicylhydrazide (XV). Gentle heating of a methanolic solution of XI with salicylaldehyde in the presence of acid gave XII. The facile hydrolysis of XI and subsequent condensation is understandable in the light of the ready hydrolysis of acethydrazide itself. McClelland and Gait (5) reported the synthesis of 2-alkylbenzisothiazolones from the dichloride (XIII) and primary amines. A reasonable extension of this reaction to salicyl-

hydrazone (XIV) resulted to a third synthesis of XII. The ultraviolet spectra of these three preparations of XII were identical.

Earlier the reaction of the acetone derivative of dithiosalicylhydrazide with pyridine and iodine *vide supra* was given as an indication that the described phenomenon was not due to *syn* and *anti* configurational transformations. The compound which was actually isolated in less than 10% yield from this reaction mixture was the saccharin derivative XVI as evidenced by the microanalytical



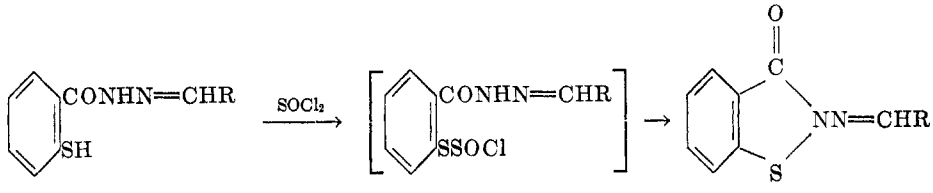
XVI



XVII

data. Subsequently an attempt was made to prepare the benzisothiazolone XVII by hydrolysis of XI in the presence of acetone. To date it has not been possible to effect this reaction or to prepare 2-aminobenzisothiazolone which could be reacted directly with acetone to yield XVII. Twenty hours' refluxing of XI dissolved in acetone utilizing equivalent amounts of either glacial acetic acid or calcium carbonate resulted in recovery of unchanged XI. When a solution of XI in ether was allowed to stand overnight in the presence of either one or two equivalents of methanolic hydrochloric acid, beautiful needles were formed which proved to be dithiosalicylhydrazide dihydrochloride. Heating XI with a molar amount of sodium carbonate in 70% aqueous methanol produced XV in 80% yield.

An alternative method for the formation of the benzisothiazolone ring system involved the reaction of thionyl chloride with the free thiol derivative, according to the following reactions:



This reaction (R = aryl) resulted in 90–95% yields of the benzisothiazolone. It has not been possible to prepare either 2-amino or 2-acetylaminobenzisothiazolone from thiosalicylhydrazide or the corresponding acetyl derivatives by this method. Evidently the presence of terminal hydrogen atoms leads to undesirable side reactions.

Early in the investigation it was observed that a mixture melting point of the disulfide and its corresponding benzisothiazolone did not consistently give the expected depression. The ultraviolet spectra of the disulfides and benzisothiaz-

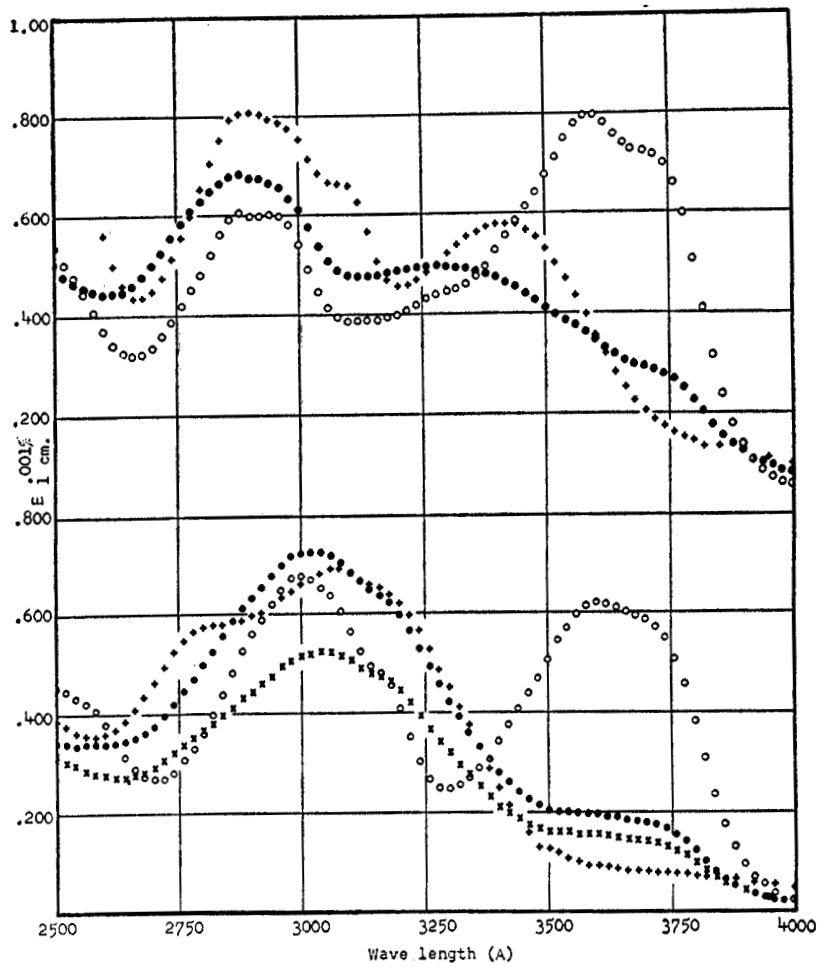


FIG. 1. THE SPECTRA WERE DETERMINED IN 0.5% DIMETHYLFORMAMIDE IN METHANOL. Upper set of curves: +++, salicylalthiosalicylhydrazide; ●●●, *bis*-(salicylal)dithiosalicylhydrazide; ○○○, 2-salicylalaminobenzthiazolone.

Lower set of curves: +++, 2,4-dichlorobenzalthiosalicylhydrazide; ●●●, *bis*-(2,4-dichlorobenzal)dithiosalicylhydrazide; ○○○, 2,4-dichlorobenzalaminobenzisothiazolone; ×××, N,N′-dibenzyldithiosalicylhydrazide.

olones are plotted in Figs. 1 and 2. Differences in the absorption between the two types of compound in the region 3600–3900 A° proved particularly useful in their characterization.

Microbiological data. In the previous communication (1) the derivatives of dithiosalicylhydrazide were reported as potent anti-bacterial and antifungal agents. The benzisothiazolones derived from these derivatives exhibited, in general, diminished bactericidal and fungicidal activity with one exception. That exception was against the microorganism *Brucella abortus* MSL 1515. In this instance the activity was enhanced by a factor of at least 2–3 and compounds

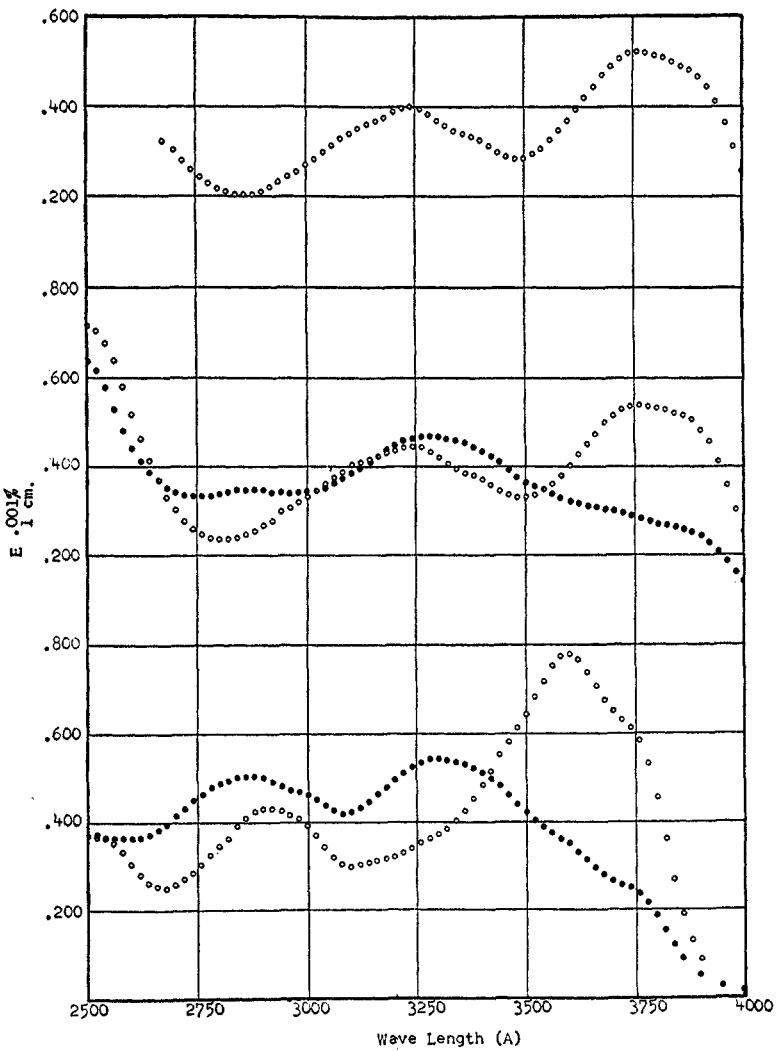


FIG. 2. UPPER CURVE: ○○○ is 2-(4-quinolalamino)-5,7-dichlorobenzisothiazolone. MIDDLE SET OF CURVES: ●●●, *bis*-(2-*n*-propoxybenzal)dithiosalicylhydrazide; ○○○, 2-*n*-propoxybenzalaminobenzisothiazolone. LOWER SET OF CURVES: ●●●, quinoline-4-aldehyde derivative of 5,5′-dichlorodithiosalicylhydrazide; ○○○, 2-(-4-quinolalamino)-5-chlorobenzisothiazolone.

1, 3, and 4, Table I, completely inhibited growth of this organism at 0.5–1.25 gamma/ml.

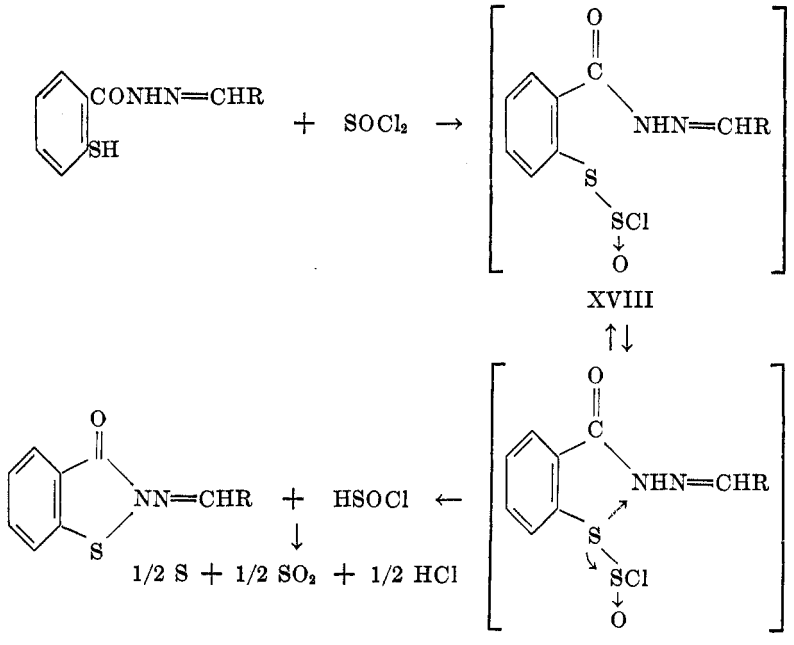
Discussion of ring closure mechanisms. In the oxidative ring closure with pyridine and iodine it is postulated that the disulfide link is cleaved to form two moles of sulfenyl iodide which in turn ring close with the propitiously situated —NH group. This would account for the quantitative yield of benzisothiazolone from a molar amount of iodine. It is well known that chlorine and bromine react with disulfides in inert solvents (6, 7) to produce sulfenyl halides but only

one case of the production of a sulfenyl iodide by this method has been recorded (8). In the present instance it is felt that excess pyridine facilitates scission of the disulfide link in the presence of iodine. Pyridine or iodine alone do not effect ring closure although iodine in the presence of a weaker base such as dimethylformamide yields 25–50% of the benzisothiazolone in three to five hours as contrasted with the instantaneous reaction with pyridine.

It has been found that other bases are capable of facilitating sulfenyl iodide formation and the reaction of iodine with the disulfide linkage in the presence of a primary or secondary base such as ethylamine or piperidine can be utilized to qualitatively titrate the amount of disulfide. In a model experiment, 2,2′-*bis*-benzthiazolyl disulfide was dissolved in methanol and four equivalents of piperidine and titrated with a methanolic solution of iodine. The theoretical amount of iodine was consumed as rapidly as it was added. When the methanolic solution was diluted with three volumes of water, the crystalline sulfenamide precipitated and was isolated. The ease of preparation of sulfenamides by this method in the laboratory indicates that it would be a useful tool for the characterization of disulfides inasmuch as one would obtain both titration data and a derivative simultaneously. The equation for the reaction is the following:

$$RSSR + I_2 + 4\ HNR'_2 \rightarrow 2\ RSNR'_2 + 2\ R'_2NH_2I$$

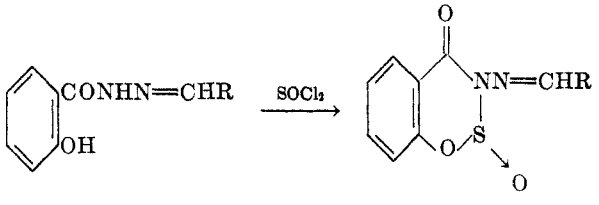
In the ring closure with thionyl chloride the following mechanism is thought to be operative:



The initial reaction is the formation of the thiosulfinyl chloride (XVIII). This intermediate, with a formal plus one charge on sulfur, undergoes polarization of

the —S—S— bond and the ring sulfur reacts electrophilically with the —NH— group. This polarization is related to that described by Archer and Suter (9) for the reaction of dithiosalicylic acid with benzene in the presence of 101% sulfuric acid. The present case differs only in that polarization is caused by an intramolecular stimulus and reaction occurs with a more electron rich source.

The question was raised concerning the possibility that N-chlorination followed by ring closure was a truer representation of the course of reaction. If this were true then the oxygen isolog (XIX) should yield a benzisoxazolone. In the reaction of XIX with thionyl chloride using the conditions outlined for I, starting material was recovered. When the reaction was run in benzene, however, the product isolated was the 1,2,3-benzoxthiazinone-4 (XX). This result corroborated the belief that the initial step was the reaction of thionyl chloride with either —SH or —OH. The addition of thionyl chloride to an hydroxyl group has recently been postulated by Cookson (10) to explain the conversion of valeroidine hydrobromide to norvaleroidine. The experimental results obtained in this investigation verify the rationality of this postulate.



XIX XX

(R = 4-chlorophenyl)

In the reaction of a benzalthiosalicylhydrazide with benzenesulfonyl chloride and potassium hydroxide a similar mechanism is involved, the postulated intermediate being a phenylthiosulfonic ester instead of the thiosulfinyl chloride.

Acknowledgment. The authors are indebted to Dr. G. B. Levy and Mr. R. Bonham for the determination of the ultraviolet spectra and to Dr. F. Carvajal and Mr. R. Hill for the microbiological results.

EXPERIMENTAL[4,5]

PREPARATION OF II

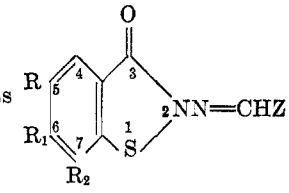
A. With benzenesulfonyl chloride and potassium hydroxide. A solution of 0.88 g. (0.005 mole) of benzenesulfonyl chloride in 10 ml. of dioxane was added dropwise to a well stirred solution of 3.25 g. (0.01 mole) of 2,4-dichlorobenzalthiosalicylhydrazide (1) and 0.66 g. (0.01 mole) of potassium hydroxide in 50 ml. of dioxane. Crystals separated as the reaction proceeded. The mixture was stirred for one-half hour after the addition was completed and then an equal quantity of water was added and the crystals were separated. There was obtained 3 g. of material melting at 240–241°. Two recrystallizations from dimethylformamide-methanol gave 2.0 g. of yellow needles, m.p. 232–234°, identical with material prepared by an iodine in pyridine oxidation.

[4] All melting points are uncorrected.

[5] Microanalyses were carried out by the Clark Microanalytical Laboratory, Urbana, Illinois.

TABLE I

2-BENZALAMINOBENZISOTHIAZOLONES



No.	R	R_1	R_2	Z	M.P., °C.	RECRYSTALLIZATION SOLVENT	ANALYSES			
							C		H	
							Calc'd	Found	Calc'd	Found
1	H	H	H	2,4-Dichlorophenyl	232–234	Dimethylformamide	52.05	52.27	2.49	2.48
2	H	H	H	3,4-Dichlorophenyl	238–239	Dimethylformamide	52.05	52.08	2.49	2.52
3	H	H	H	4-Quinolyl	212–213	Methyl Cellosolve[a]	66.83	67.05	3.63	3.79
4	H	H	H	4-Carboxyphenyl	290–292	Dimethylformamide-methanol	60.34	60.30	3.38	3.54
5	H	H	H	2-Hydroxyphenyl	242–243.5	Dimethylformamide	62.20	62.43	3.73	3.68
6	H	H	H	2-Methoxyphenyl	195–196	Ethanol	63.35	63.50	4.25	4.38
7	H	H	H	2-Ethoxyphenyl	160–162	Ethanol	64.37	64.29	4.73	4.81
8	H	H	H	2-*n*-Propoxyphenyl	115–117	Ethanol	65.30	65.49	5.16	4.97
9	H	H	H	2-*n*-Butoxyphenyl	115–116	Ethanol	66.23	66.49	5.55	5.36
10	H	H	H	2-*n*-Amyloxyphenyl	103–104	Methylcyclohexane	67.00	67.14	5.92	5.92
11	Cl	H	H	4-Quinolyl	214–216	Dimethylformamide-methanol	60.09	59.99	2.94	3.09
12	Cl	H	Cl	4-Quinolyl	253–254	Pyridine	54.60	54.52	2.42	2.47
13	H	CH_3SO_2	H	4-Quinolyl	271–272	Dimethylformamide-methanol	56.39	56.37	3.39	3.60
14	H	H	H	4-(2-Chloroethoxy)-phenyl	175–177	Aqueous Methyl Cellosolve[a]	57.74	58.24	3.94	3.65
15	H	H	H	4-(2-Diethylamino-ethoxy)phenyl hydrochloride	220	Dimethylformamide-propanol-2	59.18	59.41	5.92	5.73

[a] Methyl Cellosolve is 2-methoxyethanol.

B. With pyridine and iodine. A solution of 3.25 g. (0.01 mole) of I in 25 ml. of pyridine was treated at 5–10° with a solution of 2.54 g. (0.01 mole) of iodine in 15 ml. of pyridine. The iodine was discolored as rapidly as it was added and crystals began to separate almost immediately after the completion of the addition. Dilution of the reaction mixture with two volumes of methanol and subsequent collecting of the precipitate gave 2.8 g. of yellow needles, m.p. 232–234°.

C. With thionyl chloride. Five grams (0.015 mole) of 2,4-dichlorobenzalthiosalicylhydrazide was mixed with 25 ml. of thionyl chloride at room temperature. The benzal derivative dissolved with the evolution of hydrogen chloride to give a deep yellow solution which soon started to deposit crystals and then set to a solid mass. Ether was added to form a slurry and the crystals were collected and washed well with more ether. After drying in the oven there was obtained 4.5 g. of yellow needles, m.p. 230–232°.

Preparation of III. The synthesis of this compound by recrystallization of I or condensation of dithiosalicylhydrazide with 2,4-dichlorobenzaldehyde has been previously reported (1).

CONVERSION OF III TO II

A. With pyridine and iodine. To a solution of 3.25 g. (0.005 mole) of III in 25 ml. of pyridine, prepared by heating and then cooling, was added a solution of 1.27 g. (0.005 mole) of iodine in 10 ml. of pyridine. Crystals began to form soon after the addition was completed and 3.0 g. of material, m.p. 230–233° was isolated from the reaction mixture.

B. Heating in dimethylformamide. Compound III (250 mg.) was dissolved in 50 ml. of warm dimethylformamide and was heated at 100° for three days. After chilling to 5°, 50 mg. of light yellow needles separated, m.p. 232°, which were identical with the compound prepared by an iodine oxidation of the thiol I or disulfide III.

Diacetyl dithiosalicylhydrazide. Dithiosalicylhydrazide (20 g., 0.06 mole) (1) was dissolved in a mixture of 20 ml. of concentrated hydrochloric acid and 200 ml. of water. Then 20 ml. of acetic anhydride was added all at once at room temperature. The anhydride dissolved and the mixture warmed spontaneously to 35°. After a few seconds the mixture became cloudy and a gummy precipitate separated. The gum soon solidified and was broken up, collected, and washed with water. The yield after drying at 50° was 16 g. (64%); m.p. 254–256°, softening at 245°. The analytical sample after three recrystallizations from formamide-water melted at 264–265°.

Anal. Calc'd for $C_{18}H_{18}N_4O_4S$: C, 51.60; H, 4.33.
Found: C, 51.61; H, 4.48.

2-Acetylaminobenzisothiazolone. A solution of 6.08 g. (0.024 mole) of iodine in 30 ml. of pyridine was added dropwise at room temperature to a solution of 10 g. (0.024 mole) of diacetyldithiosalicylhydrazide in 150 ml. of dimethylformamide. The iodine was consumed as rapidly as it was added. After allowing the solution to stand for five minutes it was diluted with 600 ml. of water. The clear yellow solution soon started to deposit colorless needles. After cooling in an ice-bath for two hours the crystals were collected, washed with water, and dried at 50° to yield 6.3 g. (63.5%). The white needles after three recrystallizations from methanol-water melted at 145–147°, softening at 140° (sealed tube).

Anal. Calc'd for $C_9H_8N_2O_2S$: C, 51.90; H, 3.87.
Found: C, 51.65; H, 3.91.

PREPARATION OF XII

A. From 2-acetylaminobenzisothiazolone. A solution of 2.08 g. (0.01 mole) of XI and 1.35 g. (0.011 mole) of salicylaldehyde in 60 ml. of ethanol was prepared. This solution was heated to reflux and 2.5 ml. of concentrated hydrochloric acid was added in one portion. The solution was refluxed an additional one-half hour during which time crystals began to deposit. After chilling the reaction mixture, the solid was collected and dried at 50° to give 2.4 g. (88%), m.p. 241–243°.

B. From salicylhydrazone and thiosalicyloyl chloride-sulfenyl chloride. A stream of chlorine gas was passed through a suspension of 1.88 g. (0.007 mole) of dithiosalicyloyl chloride in 50 ml. of carbon tetrachloride as described by McClelland and Gait (5). After the solution had been freed of excess chlorine by passing nitrogen through it, it was added in a thin stream with good agitation to a cooled mixture of 1.5 g. (0.011 mole) of salicylaldehyde hydrazone, 5 ml. of dry pyridine, and 50 ml. of ethylene chloride. The precipitate which formed was washed with ethylene chloride, and water, and dried in the oven at 50°. The yield was 1.7 g. (57%), m.p. 230–232°. After recrystallization from dimethyl formamide the m.p. was raised to 242–243.5°.

C. From bis-salicylaldithiosalicylhydrazide. A solution of 4.5 g. of iodine in 15 ml. of pyridine was added to a solution of 4.5 g. of *bis*(2-hydroxybenzal)dithiosalicylhydrazide in 50 ml. of pyridine. The iodine was consumed almost immediately and a precipitate started to form after a few minutes. Three volumes of methanol were added to complete the precipitation and the crystals were collected, washed with methanol, and dried at 50° to yield 3.4 g. (76%), m.p. 244–245°.

The ultraviolet spectra of the three preparations of XII—A, B, and C—were identical within experimental error.

Bis-acetone-dithiosalicylhydrazone. Five g. (0.012 mole) of dithiosalicylhydrazide dihydrochloride was dissolved in 100 ml. of water and 10 ml. of acetone was added. The precipitation of the derivative began almost immediately and the mixture was allowed to stand at room temperature for one hour. The precipitate was collected, washed with water, and dried at 60° to yield 4.5 g. (89%) m.p. 240–242°. A sample recrystallized three times from aqueous dimethylformamide melted at 244–245°.

Anal. Calc'd for $C_{20}H_{22}N_4O_2S_2$: C, 57.92; H, 5.35.
Found: C, 57.64; H, 5.16.

Acetone thiosalicylhydrazone. A mixture of 10 ml. of acetic acid and 500 ml. of acetone was heated to the boil and 50 g. (0.297 mole) of thiosalicylhydrazide was added all at once. A small amount of an insoluble precipitate was removed and the filtrate was refluxed for one hour. After evaporating the acetone, the residue was recrystallized from aqueous propanol-2. The yield of white needles was 39 g. (63%), m.p. 120–123°. A sample recrystallized three times from aqueous propanol-2 had m.p. 127–128°.

Anal. Calc'd for $C_{10}H_{12}N_2OS$: C, 57.70; H, 5.80.
Found: C, 57.79; H, 5.64.

2-Isopropylideneaminosaccharin. A solution of 2.54 g. (0.01 mole) of iodine in 10 ml. of pyridine was added all at once, with vigorous stirring, to 2.08 g. (0.01 mole) of acetone thiosalicylhydrazone dissolved in 25 ml. of pyridine. The iodine was consumed almost at once. and very little material precipitated, indicating that there was no disulfide formation. The clear solution was diluted with ether and the precipitated pyridine hydriodide was filtered off. Extraction with water and dilute hydrochloric acid removed most of the pyridine. The clear yellow ethereal solution was dried over sodium sulfate and was evaporated to dryness on the steam-bath. The residue (100 mg.), m.p. 142–145°, was recrystallized from cyclohexane to give white needles, m.p. 150–151°.

Anal. Calc'd for $C_{10}H_{10}N_2O_3S$: C, 50.45; H, 4.20.
Found: C, 50.87; H, 3.51.

(2,4-Dichlorobenzal)thiosalicylhydrazide from 2-(2,4-dichlorobenzalamino)benzisothiazolone. A slurry of 1 g. of (2,4-dichlorobenzal)-2-aminobenzisothiazolone in 20 ml. of methanol and 20 ml. of pyridine was treated with 5 ml. of hydrazine hydrate at room temperature. The mixture became deep yellow and the benzisothiazolone dissolved within 10–15 seconds. The addition of 15 ml. of acetic acid and 65 ml. of water all at once to the yellow solution precipitated a mass of almost white crystals. The crystals were collected, washed with 30 ml. of methanol, and dried at 70° to yield 0.9 g., m.p. 214–215°.

(2,4-Dichlorobenzal)thiosalicylhydrazide from the disulfide. This reaction was carried out exactly as described above. The only observable difference was the time required for reduction. In this instance the time required was 15 minutes whereas the previous reduction was complete in 15 seconds. From 1 g. of disulfide 0.8 g. of material, m.p. 215–216° was obtained.

ATTEMPTS TO PREPARE 2-AMINOBENZISOTHIAZOLONE

A. With hydrochloric acid. A solution of 1.04 g. (0.005 mole) of XI in 7 ml. of 0.67 *N* (0.0047 mole) methanolic hydrochloric acid and 40 ml. of dry ethyl ether was allowed to stand at room temperature overnight. The white needle clusters which had formed were collected and dried at 60° to yield 600 mg., m.p. 227–228°. This material did not depress the melting point of an authentic sample of dithiosalicylhydrazide dihydrochloride and it gave an identical ultraviolet spectrum.

B. With sodium carbonate. A mixture of 208 mg. (0.001 mole) of XI, 106 mg. (0.001 mole) of sodium carbonate, 35 ml. of methanol, and 10 ml. of water was heated on a steam-bath for one-half hour. The methanol was replenished as it boiled away. The yellow solution was concentrated to 10 ml. and upon the addition of 50 ml. of ice-water a white precipitate formed. The precipitate was collected and dried at 50° to yield 170 mg. of material, m.p. 252–255°, insoluble in acid or base. One recrystallization raised the melting point to 263–265°. A mixture of this solid with an authentic sample of XV did not depress the melting point.

ATTEMPTS TO PREPARE 2-ISOPROPYLIDENEAMINOBENZISOTHIAZOLONE

A. With calcium carbonate. A mixture of 208 mg. (0.001 mole) of XI, 100 mg. (0.001 mole) of calcium carbonate, and 50 ml. of acetone was refluxed for 20 hours and filtered from the solid. The filtrate was evaporated to dryness and the residue was crystallized from aqueous methanol to give 165 mg. of solid, m.p. 150–153°, indistinguishable from XI by mixture m.p. or ultraviolet spectra.

B. With glacial acetic acid. A mixture of 208 mg. (0.001 mole) of XI, 0.5 ml. of glacial acetic acid, and 50 ml. of acetone was treated as described in the preceding experiment. Unchanged starting material was recovered.

3-(4-Chlorobenzalamino)-1,2,3-benzoxthiazinone-4. Into a 250 ml. three-necked flask equipped for refluxing and stirring were placed 5.0 g. (0.0182 mole) of 4-chlorobenzalsalicylhydrazide, 12.0 g. (0.10 mole) of thionyl chloride, and 40 ml. of benzene. The suspension was stirred and heated to gentle reflux in 15 minutes. After 45 minutes, a clear yellow solution was obtained which was maintained at reflux an additional one-half hour. The solution was chilled in an ice-bath, diluted with two volumes of cyclohexane, and the precipitate was collected. The needles were washed with 100 ml. of cyclohexane and dried at 60° to yield 4.7 g. (81%), m.p. 172–174°. A sample recrystallized from a benzene-cyclohexane mixture separated as long needles; m.p. 177–178°.

Anal. Calc'd for $C_{14}H_9ClN_2O_3S$: C, 52.41; H, 2.80; S, 9.98.
Found: C, 52.91; H, 2.89; S, 10.03.

2-Benzthiazolylsulfenpiperide. Into a 250-ml. flask were placed 3.32 g. (0.01 mole) of *bis*-benzthiazolyl disulfide, 3.5 g. (0.04 mole) of piperidine, and 15 ml. of methanol. To this solution was added a solution of 2.57 g. (0.01 mole) of iodine in 30 ml. of methanol. The color of iodine was discharged as rapidly as it was added and the resulting light yellow solution was allowed to stand for one-half hour. Dilution of this solution with 150 ml. of water caused the precipitation of a white solid, m.p. 75–77°. This material was identified as the sulfenpiperidide originally prepared by Tschunkur and Kohler (12), m.p. 80°.

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SUMMARY

Three new methods for the preparation of 2 substituted aminobenzisothiazolones have been described: treatment of thiosalicylhydrazones (a) with pyridine and iodine (b) with benzenesulfonyl chloride and potassium hydroxide, and (c) with thionyl chloride.

Reaction of 4-chlorobenzalsalicylhydrazide with thionyl chloride resulted in the formation of a benzoxthiazinone (XX).

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