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Fused-Ring Systems Containing 1,2,4-Benzothiadiazines. II. Reactions of *o*-Amino-*N*-hydroxybenzenesulfonamides.

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o-Amino-*N*-hydroxybenzenesulfonamides have been treated with aldehydes to prepare 2-hydroxy-1,2,4-benzothiadiazine 1,1-dioxides. These products have permitted the fusion of an additional ring to the "b" face of the benzothiadiazine. Analogs of the tricyclic compounds have been made in other ways.

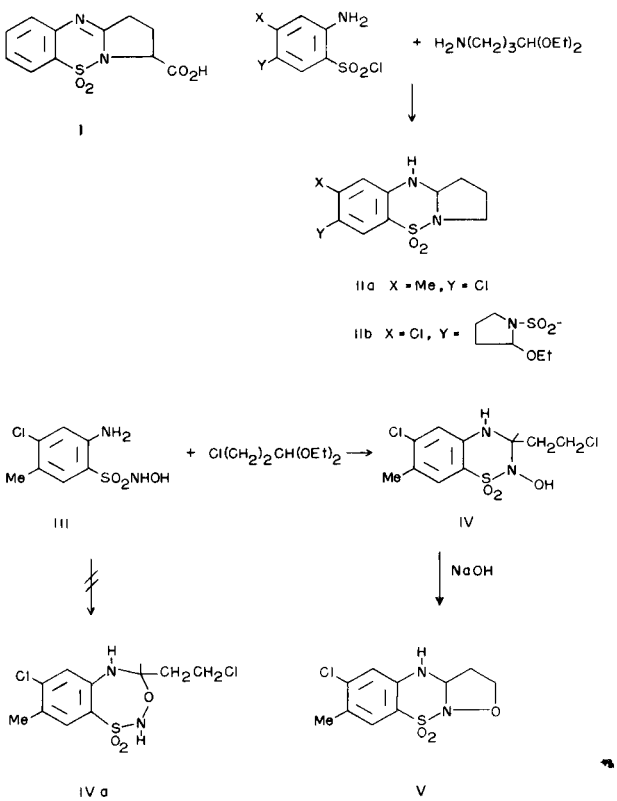
We recently described (1) the preparation of 1,2,4-benzothiadiazine 1,1-dioxides having additional rings fused at the "c" face. It seemed of interest to continue this examination and we wish to report on the synthesis of benzothiadiazines and related materials having an additional ring fused at the "b" face.

A recent report (2) has described the preparation in several steps of 2,3-dihydro-1*H*-pyrrolo[1,2-b]-[1,2,4]benzothiadiazine-3-carboxylic acid 5,5-dioxide (I) and related compounds. We have achieved a one-step preparation of 2,3,10,10a-tetrahydro-1*H*-pyrrolo[1,2-b][1,2,4]benzothiadiazine 5,5-dioxides (II) by treatment of *o*-aminobenzenesulfonyl chlorides with γ-aminobutyraldehyde diethyl acetal. When a second chlorosulfonyl function was present but not adjacent to an amino group, a 2-ethoxypyrrolidinyl-sulfonyl function was found in the product after reaction with the aminoacetal.

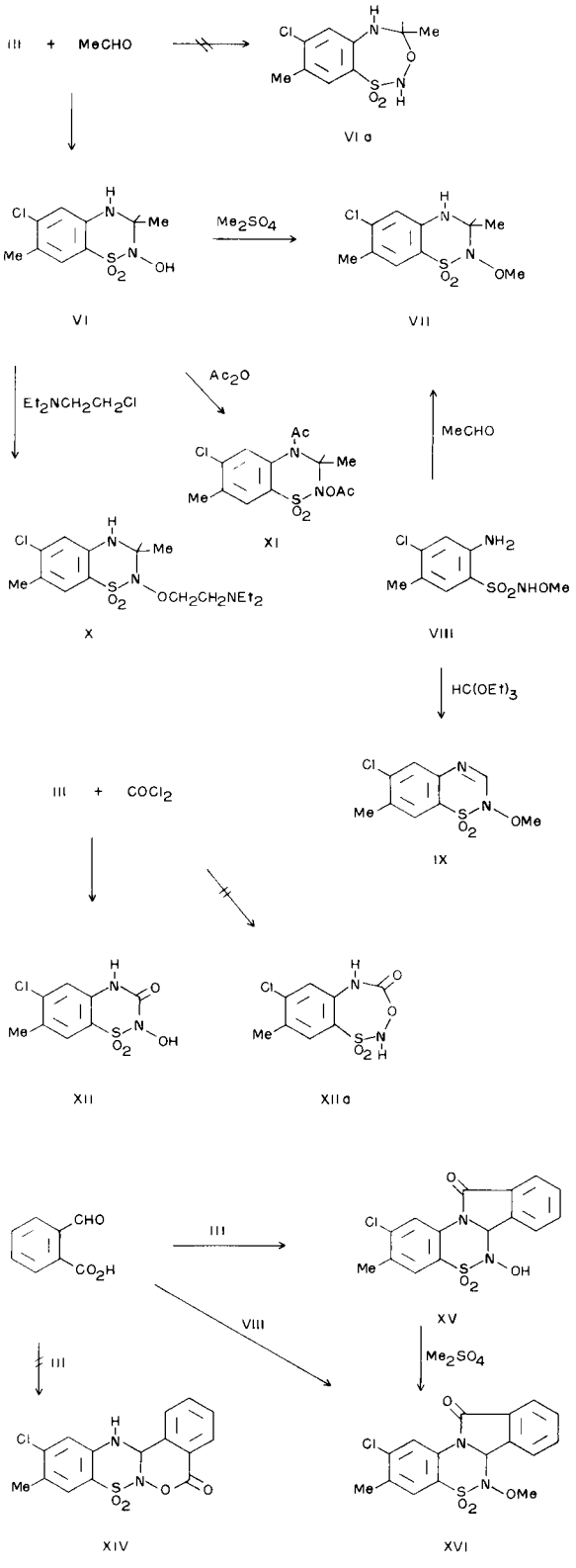
Compounds similar to II but having a second heteroatom in the "b" fused ring (3) were of interest. An example of such a compound is the isoxazolo-[2,3-b][1,2,4]benzothiadiazine (V). For the synthesis of V, 6-amino-4-chloro-*m*-toluenesulfonhydroxamic acid (III) was first treated with β-chloropropionaldehyde diethyl acetal, to afford 6-chloro-3-(2-chloroethyl)-3,4-dihydro-2-hydroxy-7-methyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (IV). Alkali served to convert IV into 6-chloro-2,3,3a,4-tetrahydro-7-methylisoxazolo[2,3-b][1,2,4]benzothiadiazine 9,9-dioxide (V).

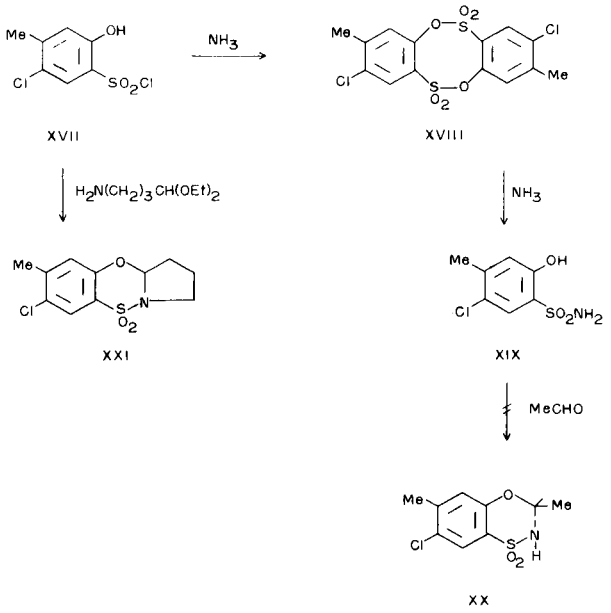
Since the reaction of an *o*-amino-*N*-hydroxybenzenesulfonamide with an aldehyde might have produced the seven-membered 3,1,2,5-benzoxathiadiazepine ring (IVa), studies were undertaken to verify the structures of IV and V by investigating simpler compounds resulting from the reactions of III with non-halogenated aldehydes and acids. For example, reaction of III with acetaldehyde gave VI and the product was methylated to give 6-chloro-3,4-dihydro-2-methoxy-3,7-dimethyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (VII). The possibility of VI being the isomeric 7-chloro-4,5-dihydro-4,8-dimethyl-3,1,2,5-2*H*-benzoxathiadiazepine 1,1-dioxide (VIa) was eliminated by an alternative preparation of VII from acetaldehyde and 6-amino-4-chloro-*N*-methoxy-*m*-toluenesulfonamide (VIII), itself synthesized from the reaction of methoxyamine and 6-amino-4-chloro-*m*-toluenesulfonylchloride. An unsaturated relative of VII (IX) was obtained by allowing VIII to react with triethyl orthoformate. The n.m.r. spectra (deuteriochloroform) of VII and IX showed methoxy singlets at δ 3.84 and 4.23, respectively.

Alkylation of VI by diethylaminoethyl chloride was carried out to give X and acetylation of VI afforded



2-acetoxy-4-acetyl-6-chloro-3,4-dihydro-3,7-dimethyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (XI). The infrared spectrum of XI indicated the presence of both an amide function (5.9 μ) and an *N*-acetoxy function (5.6 μ).





Phosgene reacted with III to give 6-chloro-2-hydroxy-7-methyl-2*H*-1,2,4-benzothiadiazin-3(4*H*)-one 1,1-dioxide (XII) (IR peak at 5.85 μ). None of the isomeric 7-chloro-8-methyl-3,1,2,5-2*H*-benzoxathiadiazepin-4(5*H*)-one 1,1-dioxide (XIIa) was found, consistent with the failure to obtain a seven-membered ring compound from the treatment of III with acetaldehyde. Acetylation of XII gave the 2-acetoxy derivative (XIII) (IR peaks at 5.5 μ and 5.9 μ).

An attempt to prepare an isoxazine "b" fused product (XIV) by causing III to react with phthalaldehydic acid gave instead a "c" fused product (XV). The structure of XV was confirmed by its methylation product XVI which was identical with the reaction product from VIII and phthalaldehydic acid. This might have been expected from our earlier work (1). That the product was XV was further supported by the carbonyl stretching peak (5.90 μ). Absorption at shorter wave length would be expected for the alternative structure (XIV).

It seemed possible to prepare compounds analogous to II, but having oxygen in the middle ring. Since even the simple benzoxathiazine dioxides do not appear to have been studied it was desirable first to prepare these simpler compounds. The chlorosulfonation of 4-chloro-*m*-cresol at 0° afforded 5-chloro-2-hydroxy-*p*-toluenesulfonyl chloride (XVII). Compound XVII upon treatment with ammonia gave the dimeric sulfonate ester XVIII (4). Prolonged treatment with ammonia afforded the expected 5-chloro-2-hydroxy-*p*-toluenesulfonamide (XIX).

Acetaldehyde did not convert XIX into 7-chloro-2,3-dihydro-3,6-dimethyl-4,1,2-benzoxathiazine 1,1-dioxide (XX). However, treatment of XVII with γ-aminobutyraldehyde diethyl acetal, resulted in 7-chloro-8-methyl-1,2,3,10a-tetrahydropyrrolo[1,2-b]-[4,1,2]benzoxathiazine 5,5-dioxide (XXI).

EXPERIMENTAL (5)

7-Chloro-2,3,10,10a-tetrahydro-8-methyl-1*H*-pyrrolo[1,2-b][1,2,4]-benzothiadiazine 5,5-dioxide (IIa).

A solution of 3 g. of 2-amino-5-chloro-*p*-toluenesulfonyl chloride in 50 ml. of dimethoxyethane was added to a solution of 2 g. of γ-aminobutyraldehyde diethyl acetal and 2 g. of triethylamine in 50 ml. of dimethoxyethane. The reaction mixture became warm and slightly colored. After 10 minutes the reaction mixture was diluted with water and acidified with hydrochloric acid. On cooling, there precipitated 1.7 g. of solid which was recrystallized from alcohol. Compound IIa melted at 214-216°.

Anal. Calcd. for $C_{11}H_{13}ClN_2O_2S$: C, 48.42; H, 4.80; N, 10.27; Cl, 13.0; S, 11.7. Found: C, 48.13; H, 4.68; N, 9.74; Cl, 13.2; S, 11.4.

8-Chloro-7-(2-ethoxy-1-pyrrolidinylsulfonyl)-2,3,10,10a-tetrahydro-1*H*-pyrrolo[1,2-b][1,2,4]benzothiadiazine 5,5-dioxide (IIb).

A dimethoxyethane solution of 6.5 g. of 4-amino-6-chloro-1,3-benzenedisulfonyl chloride was slowly added to a cold solution of 5.8 g. of γ-aminobutyraldehyde diethyl acetal in 150 ml. of dimethoxyethane containing 4 g. of triethylamine. The mixture was stirred for 10 minutes diluted with water and extracted with chloroform. The chloroform extract was dried over magnesium sulfate. The solution was concentrated and the residue was dissolved in ethanol. After a few drops of hydrochloric acid were added, the solution was warmed on a steam bath for 10 minutes. The resultant solid (7.9 g.) was collected and recrystallized from a mixture of dimethoxyethane and ethanol to give IIb, m.p. 170-172°.

Anal. Calcd. for $C_{16}H_{22}ClN_3O_5S_2$: C, 44.09; H, 5.09; Cl, 8.1; N, 9.64; S, 14.7. Found: C, 44.42; H, 5.11; Cl, 8.1; N, 9.51; S, 14.0.

6-Amino-4-chloro-*N*-hydroxy-*m*-toluenesulfonamide (III).

A solution of 48 g. of 6-amino-4-chloro-*m*-toluenesulfonyl chloride in 300 ml. of dioxane was slowly added to a cold aqueous solution of 28 g. of hydroxylamine hydrochloride and 44 g. of triethylamine. The solution was kept at room temperature overnight and concentrated *in vacuo*. The residue was diluted with water and the precipitate was collected, washed with water and dried at room temperature (7.5 g.). Recrystallization from aqueous alcohol afforded material melting at 165-167° dec.

Anal. Calcd. for $C_7H_9ClN_2O_3S$: C, 35.51; H, 3.83; Cl, 15.0; N, 11.84; S, 13.6. Found: C, 35.70; H, 3.93; Cl, 14.6; N, 11.60; S, 13.2.

6-Chloro-3-(2-chloroethyl)-3,4-dihydro-7-methyl-2-hydroxy-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (IV).

A solution of III (5.3 g.) and β-chloropropionaldehyde, diethyl acetal, (4.5 g.) in 100 ml. of ethanol containing 3 drops of concentrated hydrochloric acid was warmed on a steam bath for 15 minutes. The solution was treated with charcoal, filtered and the solvent was removed *in vacuo*. The residue was recrystallized from benzene to yield 1.3 g. of IV, m.p. 134-145°.

Anal. Calcd. for $C_{10}H_{12}ClN_2O_3S$: C, 38.59; H, 3.89; Cl, 22.8; N, 9.00; S, 10.3. Found: C, 38.83; H, 3.89; Cl, 22.4; N, 8.96; S, 10.0.

6-Chloro-7-methyl-2,3,3a,4-tetrahydroisoxazolo[2,3-b][1,2,4]benzothiadiazine 9,9-dioxide (V).

To a cold solution of 6 g. of IV and 0.5 g. of sodium iodide in 300 ml. of acetone was slowly added a solution of 5 g. of sodium hydroxide in 20 ml. of water. The mixture was stirred in an ice bath for 2 hours. The acetone layer was decanted and the aqueous solution was further extracted with acetone. The combined acetone extracts were dried over magnesium sulfate and the solvent was removed *in vacuo*. The residue was recrystallized from a mixture of ethanol and dimethoxyethane, yielding 2.4 g. of V, m.p. 199-200°.

Anal. Calcd. for $C_{10}H_{11}ClN_2O_3S$: C, 43.71; H, 4.03; Cl, 12.9; N, 10.20; S, 11.7. Found: C, 43.86; H, 4.03; Cl, 12.6; N, 10.21; S, 11.2.

6-Chloro-3,7-dimethyl-2-hydroxy-3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (VI).

Four grams of III was dissolved in 100 ml. of ethanol and to the solution 4 g. of acetaldehyde was gradually added. The mixture was heated on a steam bath for 1 hour and treated with charcoal. The solvent was removed *in vacuo* and benzene was added to the residue to give a white solid (3 g.) which was collected and recrystallized from a mixture of ethanol and cyclohexane. Compound VI had m.p. 214-216° dec.

Anal. Calcd. for $C_9H_{11}ClN_2O_3S$: C, 41.15; H, 4.21; Cl, 13.5; N, 10.67; S, 12.2. Found: C, 41.02; H, 4.13; Cl, 13.5; N, 10.80; S, 12.2.

6-Chloro-3,4-dihydro-3,7-dimethyl-2-methoxy-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (VII).

Compound VI (1 g.) was suspended in 100 ml. of aqueous acetone containing 1 g. of sodium hydroxide. With stirring and cooling 1 ml. of dimethylsulfate was gradually added and stirring was continued for 1 hour. The precipitate (0.5 g.) was recrystallized from benzene to give VII, m.p. 211-213° dec.

Anal. Calcd. for $C_{10}H_{13}ClN_2O_3S$: C, 43.40; H, 4.74; Cl, 12.8; N, 10.13; S, 11.6. Found: C, 43.59; H, 4.65; Cl, 12.8; N, 10.12; S, 11.7.

6-Amino-4-chloro-*N*-methoxy-*m*-toluenesulfonamide (VIII).

6-Amino-4-chloro-*m*-toluenesulfonyl chloride (12 g.) in 100 ml. of dimethoxyethane was slowly added to 5 g. of methoxyamine hydrochloride in 50 ml. of aqueous dimethoxyethane (1:1). To the mixture 12 g. of triethylamine was slowly added with cooling. The mixture was stirred for 1 hour. Benzene (300 ml.) was added to the mixture and the benzene layer was separated and washed with water. After drying over magnesium sulfate the solvent was removed *in vacuo*. The crude residue (5.2 g.) was recrystallized from benzene to afford VIII, m.p. 124-125°.

Anal. Calcd. for $C_8H_{11}ClN_2O_3S$: C, 38.30; H, 4.43; Cl, 14.2; N, 11.17; S, 12.8. Found: C, 38.50; H, 4.36; Cl, 14.7; N, 11.15; S, 12.6.

6-Chloro-7-methyl-2-methoxy-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (IX).

Compound VIII (3.8 g.) was dissolved in 35 ml. of triethyl orthoformate and heated to 120° during 0.5 hour, while the alcohol which was generated was distilled off. The temperature was raised to 180° for 2.5 hours. The yellow solid which separated upon cooling was collected and washed with ethanol. Recrystallization from ethanol gave 2.2 g. of IX, m.p. 171-173°.

Anal. Calcd. for $C_9H_9ClN_2O_3S$: C, 41.40; H, 3.48; Cl, 13.6; N, 10.73; S, 12.3. Found: C, 41.59; H, 3.37; Cl, 13.7; N, 10.62; S, 12.0.

6-Chloro-2-(2-diethylaminoethoxy)-3,7-dimethyl-3,4-dihydro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide hydrochloride (X).

Solutions of 3.5 g. of VI in 200 ml. of acetone and 2.7 g. of sodium hydroxide in 5 ml. of water were mixed and with stirring and cooling 4.6 g. of diethylaminoethyl chloride hydrochloride was added. After stirring for 4 hours, the acetone layer was separated and the aqueous portion was extracted with acetone. The combined extracts were concentrated *in vacuo* and the residue was taken up in ether and thoroughly dried over magnesium sulfate. Alcoholic hydrogen chloride was added to form the hydrochloride of X. After recrystallization from dimethoxyethane, there was obtained 2.5 g. of X·HCl, m.p. 110°.

Anal. Calcd. for $C_{15}H_{24}ClN_3O_3S\cdot HCl$: C, 45.23; H, 6.32; Cl, 17.8; N, 10.55; S, 8.1. Found: C, 45.10; H, 6.29; Cl, 17.5; N, 10.31; S, 8.1.

2-Acetoxy-4-acetyl-6-chloro-3,4-dihydro-3,7-dimethyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (XI).

Six grams of VI in 200 ml. of chloroform was heated on the steam bath with 25 ml. of acetic anhydride until solution was complete. Water was cautiously added to the cooled solution to decompose excess anhydride. The chloroform layer was separated, dried and concentrated. The residue was recrystallized from benzene, giving 1.9 g. of XI, m.p. 162-163° dec.

Anal. Calcd. for $C_{13}H_{15}ClN_2O_5S$: C, 45.02; H, 4.36; Cl, 10.2; N, 8,08; S, 9.3. Found: C, 45.61; H, 4.33; Cl, 10.1; N, 7.77; S, 9.2.

6-Chloro-2-hydroxy-7-methyl-2*H*-1,2,4-benzothiadiazin-3(4*H*)-one 1,1-dioxide (XII).

With stirring and cooling a solution of 2.4 g. of phosgene in 30 ml. of dimethoxyethane was added dropwise to a solution of 5.2 g. of III in 100 ml. of dimethoxyethane. After stirring for 3 hours a small amount of insoluble material was filtered off and the filtrate was concentrated *in vacuo*. The oily residue was treated with benzene whereupon it crystallized. The product (3.4 g.) was collected and recrystallized from a mixture of dimethoxyethane and benzene giving XII, m.p. 205-207° dec.

Anal. Calcd. for $C_8H_7ClN_2O_4S$: C, 36.58; H, 2.69; Cl, 13.5; N, 10.67; S, 12.2. Found: C, 36.42; H, 2.85; Cl, 13.7; N, 11.03; S, 12.3.

2-Acetoxy-6-chloro-7-methyl-2*H*-1,2,4-benzothiadiazin-3(4*H*)-one 1,1-dioxide (XIII).

A solution of 2 g. of XII in 7 ml. of acetic anhydride was heated on a steam bath for 2 hours. The excess reagent was removed *in vacuo* and the residue was recrystallized from benzene. Compound XIII (1.1 g.) had m.p. 209-211°.

Anal. Calcd. for $C_{10}H_9ClN_2O_5S$: C, 39.41; H, 2.98; Cl, 11.6; N, 9.20; S, 10.5. Found: C, 39.69; H, 3.14; Cl, 11.6; N, 9.43; S, 10.7.

2-Chloro-6,6a-dihydro-6-hydroxy-3-methyl-11*H*-isoindolo[1,2-c][1,2,4]-benzothiadiazin-11-one 5,5-dioxide (XV).

Reflux of a solution of 6 g. of III and 3.4 g. of phthalaldehydic acid and two drops of concentrated sulfuric acid in 200 ml. of dimethoxyethane was carried on for 3 hours. The solution was filtered and concentrated to afford 7.4 g. of XV, m.p. 298-300°.

Anal. Calcd. for $C_{15}H_{11}ClN_2O_4S$: C, 51.35; H, 3.15; Cl, 10.1; N, 7.99; S, 9.1. Found: C, 51.58; H, 2.92; Cl, 10.1; N, 7.78; S, 9.1.

2-Chloro-6,6a-dihydro-6-methoxy-3-methyl-11*H*-isoindolo[1,2-c][1,2,4]-benzothiadiazin-11-one 5,5-dioxide (XVI).

Compound XVI was prepared from 7.4 g. of VIII and 5.2 g. of phthalaldehydic acid as described above for XV. The product, 4 g., after recrystallization from ethanol, melted at 169-170°.

An identical material was obtained by methylation of XV as described above in the preparation of VII.

Anal. Calcd. for $C_{16}H_{13}ClN_2O_4S$: C, 52.67; H, 3.59; Cl, 9.7; N, 7.68; S, 8.8. Found: C, 52.84; H, 3.45; Cl, 9.7; N, 7.92; S, 9.2.

5-Chloro-2-hydroxy-*p*-toluenesulfonyl chloride (XVII).

To 380 ml. of chlorosulfonic acid (cooled in an ice-salt bath) was slowly added 130 g. of 4-chloro-*m*-cresol. The mixture was stirred in the ice bath for 0.5 hour and poured onto cracked ice. The mixture was stirred with 2000 ml. of benzene. The benzene solution was washed with water and dried over magnesium sulfate. After removal of benzene the residue was recrystallized from hexane to afford 50 g. of XVII, m.p. 59-60°.

Anal. Calcd. for $C_7H_6Cl_2O_3S$: C, 34.86; H, 2.51. Found: C, 35.29; H, 2.60.

2,8-Dichloro-3,9-dimethyldibenzo[1,5,2,6]dioxadithiocin-6,6,12,12-tetroxide (XVIII).

Ten grams of XVII was gradually added to 100 ml. of concentrated ammonium hydroxide and the mixture was stirred at room temperature for 0.5 hour. The product was collected and recrystallized from dimethoxyethane giving white crystals, 4 g., m.p. 315-318°.

Anal. Calcd. for $C_{14}H_{10}Cl_2O_6S_2$: C, 41.09; H, 2.46; Cl, 17.3; S, 15.7. Found: C, 41.41; H, 2.49; Cl, 17.3; S, 15.3.

5-Chloro-2-hydroxy-*p*-toluenesulfonamide (XIX).

Compound XVIII (20 g.) was heated under reflux for 8 hours in 200 ml. of concentrated ammonium hydroxide and 200 ml. of ethanol. The solution was evaporated and the residue was recrystallized from aqueous ethanol and from a mixture of benzene and ethanol. Five grams of XIX, m.p. 210° dec., was obtained.

Anal. Calcd. for $C_7H_8ClNO_3S$: C, 37.91; H, 3.64; N, 6.32. Found: C, 38.08; H, 3.61; N, 6.38.

7-Chloro-8-methyl-1,2,3,10a-tetrahydropyrrolo[1,2-b][4,1,2]benzoxathiazine 5,5-dioxide (XXI).

To a cold dimethoxyethane solution (100 ml.) of 3.3 g. of γ-aminobutyraldehyde diethyl acetal containing 2.5 g. of triethylamine was slowly added 5 g. of XVII. The mixture was heated in a water bath for 2 hours. Water (300 ml.) was added and the mixture was extracted with benzene. The benzene solution was dried over magnesium sulfate and was concentrated *in vacuo*. The residue was taken up in ethanol and a small amount of insoluble material was filtered off.

The filtrate was acidified with hydrochloric acid, heated on a steam bath for 15 minutes and concentrated. The residue upon removal of alcohol was dissolved in benzene. The benzene solution was washed with water, dried over magnesium sulfate and concentrated. The residue was recrystallized from cyclohexane giving 2 g. of XXI, m.p. 135-137°.

Anal. Calcd. for $C_{11}H_{12}ClNO_3S$: C, 48.26; H, 4.42; Cl, 13.0; N, 5.12; S, 11.7. Found: C, 48.45; H, 4.57; Cl, 12.9; N, 4.87; S, 11.4.

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