

# Studies on Hypoglycemic Agents. IV.<sup>1)</sup> Synthesis of 1,4,3-Benzoxathiazine-4,4-dioxides

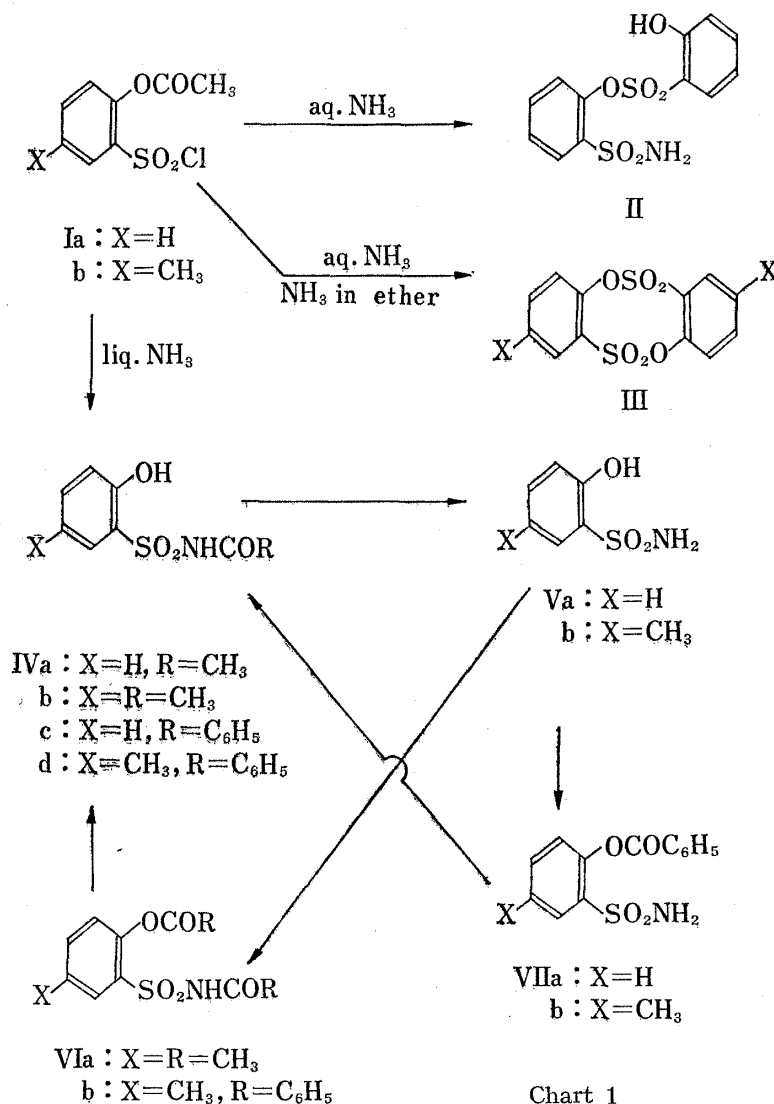
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2-Hydroxybenzenesulfonamides were prepared in good yield from 2-acetoxyphenyl-sulfonylchlorides *via* N-acetyl-2-hydroxybenzenesulfonamides, followed by hydrolysis. The preparations of 2-alkyl, aryl, benzyl, or substituted amino-1,4,3-benzoxathiazine-4,4-dioxides were described. Further 2-methyl-, or benzyl-2,3-dihydro-1,4,3-benzoxathiazine-4,4-dioxide was also prepared.

In the course of an investigation of hypoglycemic agents, it was necessary to synthesize 1,4,3-benzoxathiazine-4,4-dioxide derivatives.

1) Part III: *Yakugaku Zasshi*, **84**, 1024 (1964).

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By a survey of the literature, the synthetic method for 1,4,3-benzoxathiazine-4,4-dioxide and its derivatives (VIII) do not appear to have been studied but 2-phenyl-1,4,3-benzoxathiazine-4,4-dioxide was obtained by Wertheim,<sup>3)</sup> in the course of the preparation of diphen-saccharin derivative, by the diazotization of 2-benzoylsulfamoylaniline, followed by the loss of nitrogen and ring closure

The authors attempted to synthesize VIII from 2-hydroxybenzenesulfonamide as illustrated in Chart 2.

Concerning 2-hydroxybenzenesulfonamides (V), there was the report in which Raffa<sup>4)</sup> obtained V(X=H) by the diazotization of 2-aminobenzenesulfonamide. However Bartram, *et al.*<sup>5)</sup> reported that Raffa's compound was 2-aminophenylsulfonic acid, and then 2-hydroxybenzenesulfonamide could be obtained from 2-benzyloxyaniline by conversion *via* the diazonium salt into 2-benzyloxyphenylsulfonyl chloride and hence into the sulfonamide, followed by catalytic debenzoylation. Further, he described that reaction of 2-acetoxypheylsulfonyl chloride (I, X=H) with aqueous ammonia gave a compound, probably 2-(2-hydroxyphenylsulfonyloxy)benzenesulfonamide (II) as sole product. Anschütz<sup>6)</sup> reported that reaction of I with anhydrous ammonia in ether gave dimeric sulfonylester, dibenzo-1,5,2,6-dioxadithiocin-6,6,12,12-tetraoxides (III). Recently Wei, *et al.*<sup>7)</sup> obtained 5-chloro-2-hydroxy-*p*-toluenesulfonamide from the corresponding dimeric sulfonylester, prepared by the treatment of 5-chloro-2-hydroxytoluenesulfonyl chloride with aqueous ammonia, by prolonged treatment with aqueous ammonia. From above description, it is seemed that the compound (II) resulted *via* the corresponding dimeric ester, followed by a partial ammonolysis, therefore prolonged treatment of II with ammonia may give 2-hydroxybenzenesulfonamide (Va).

TABLE I. Analytical Data of Compound IV, VI, and VII

| No.  | Formula                                           | Analysis (%) |      |      |       |      |      | IR $\nu_{\max}$ cm <sup>-1</sup><br>in KBr-Tablet |       |
|------|---------------------------------------------------|--------------|------|------|-------|------|------|---------------------------------------------------|-------|
|      |                                                   | Calcd.       |      |      | Found |      |      | -CO-N                                             | -CO-O |
|      |                                                   | C            | H    | N    | C     | H    | N    |                                                   |       |
| IVa  | C <sub>8</sub> H <sub>9</sub> O <sub>4</sub> NS   | 44.66        | 4.22 | 6.51 | 44.61 | 4.08 | 6.10 | 1680                                              | —     |
| IVb  | C <sub>9</sub> H <sub>11</sub> O <sub>4</sub> NS  | 47.16        | 4.84 | 6.11 | 47.25 | 4.91 | 5.56 | 1685                                              | —     |
| IVc  | C <sub>13</sub> H <sub>11</sub> O <sub>4</sub> NS | 56.32        | 4.00 | 5.05 | 56.59 | 3.97 | 4.98 | 1690                                              | —     |
| IVd  | C <sub>14</sub> H <sub>13</sub> O <sub>4</sub> NS | 57.73        | 4.50 | 4.82 | 57.75 | 4.53 | 4.29 | 1655                                              | —     |
| VIa  | C <sub>11</sub> H <sub>13</sub> O <sub>5</sub> NS | 48.71        | 4.83 | 5.16 | 48.71 | 4.75 | 4.86 | 1675                                              | 1770  |
| VIb  | C <sub>21</sub> H <sub>17</sub> O <sub>5</sub> NS | 63.79        | 4.33 | 3.54 | 64.19 | 4.59 | 3.42 | 1690                                              | 1730  |
| VIIa | C <sub>13</sub> H <sub>11</sub> O <sub>4</sub> NS | 56.32        | 4.00 | 5.05 | 55.92 | 4.22 | 4.66 | —                                                 | 1720  |
| VIIb | C <sub>14</sub> H <sub>13</sub> O <sub>4</sub> NS | 57.73        | 4.50 | 4.82 | 57.63 | 4.44 | 4.54 | —                                                 | 1720  |

The present authors have been interested in the reactivities of I. And it was found that the treatment of I with liquid ammonia gave N-acetyl 2-hydroxybenzenesulfonamide (IV) in good yield, as the results of amidation and O→N rearrangement of acetyl group, without formation of the dimeric sulfonylester (III) or the sulfonyloxy sulfonamide (II). Compound (IV) was quantitatively hydrolyzed to V. It is of deep interest that I reacted with aqueous ammonia or dry ammonia in ether to give dimeric sulfonylester, while with liquid ammonia to give sulfonamide.

3) E. Wertheim, *J. Am. Chem. Soc.*, **56**, 971 (1934).

4) L. Raffa, *Farmaco (Pavia) Ed. Sci.*, **10**, 532 (1955) (*C.A.*, **50**, 8509a (1956)).

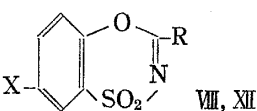
5) C.A. Bartram, P. Oxley, D.A. Peak, and J.S. Nicholson, *J. Chem. Soc.*, **1958**, 2903.

6) R. Anschütz, *Ann.*, **415**, 65 (1918).

7) P.H.L. Wei, S.C. Bell, and S.J. Childress, *J. Hetrocyclic Chem.*, **3**, 1 (1966).



TABLE II.



VIII, XII

| No.   | X               | R                                                                                     | mp<br>(°C) | Recryst.<br>solvent | Appearance  | Prepd. from                 | Yield<br>(%) |
|-------|-----------------|---------------------------------------------------------------------------------------|------------|---------------------|-------------|-----------------------------|--------------|
| VIIIa | H               | CH <sub>2</sub> Ph                                                                    | 157—158    | EtOH                | plates      | Va + PhCH <sub>2</sub> COCI | 62           |
| b     | CH <sub>3</sub> | CH <sub>2</sub> Ph                                                                    | 151—152    | EtOH                | prisms      | Vb + PhCH <sub>2</sub> COCI | 58           |
| c     | H               | CH <sub>3</sub>                                                                       | 179—182    | EtOH                | needles     | IVa                         | 36           |
| d     | CH <sub>3</sub> | CH <sub>3</sub>                                                                       | 183—184    | EtOH                | long plates | IVb                         | 67           |
| e     | H               | Ph                                                                                    | 176—177    | EtOH                | needles     | Va + PhC(OMe) <sub>3</sub>  | 92           |
| f     | CH <sub>3</sub> | Ph                                                                                    | 212—214    | EtOH                | needles     | Vb + PhC(OMe) <sub>3</sub>  | 96           |
| g     | H               | C <sub>2</sub> H <sub>5</sub>                                                         | 117—118    | Xylene              | long plates | Va + EtC(OEt) <sub>3</sub>  | 92           |
| h     | CH <sub>3</sub> | C <sub>2</sub> H <sub>5</sub>                                                         | 154        | Benzene             | long plates | Vb + EtC(OEt) <sub>3</sub>  | 94           |
| i     | H               | H                                                                                     | 161—164    | Benzene             | needles     | Xa                          | 17           |
| j     | CH <sub>3</sub> | H                                                                                     | 166—169    | Benzene             | long plates | Xb                          | 25           |
| XIIa  | H               | HN-  | 209—212    | MeCN                | needles     | XIIa                        | 39           |
| b     | CH <sub>3</sub> | HN-  | 173—176    | MeCN                | needles     | XIIb                        | 44           |
| c     | CH <sub>3</sub> | NHPh                                                                                  | 271—272    | EtOH                | needles     | XIIc                        | 43           |

| No.  | Formula                                           | Analysis (%) |      |       |       |      |      | IR $\nu_{\max}$ cm <sup>-1</sup><br>in<br>KBr-Tablet<br>-C=N- |
|------|---------------------------------------------------|--------------|------|-------|-------|------|------|---------------------------------------------------------------|
|      |                                                   | Calcd.       |      |       | Found |      |      |                                                               |
|      |                                                   | C            | H    | N     | C     | H    | N    |                                                               |
| VIIa | C <sub>14</sub> H <sub>11</sub> O <sub>3</sub> NS | 61.54        | 4.06 | 5.13  | 61.87 | 4.38 | 5.43 | 1640                                                          |
| b    | C <sub>15</sub> H <sub>13</sub> O <sub>3</sub> NS | 62.71        | 4.56 | 4.88  | 62.75 | 4.85 | 5.04 | 1630                                                          |
| c    | C <sub>8</sub> H <sub>7</sub> O <sub>3</sub> NS   | 48.74        | 3.58 | 7.11  | 49.00 | 3.58 | 6.87 | 1630                                                          |
| d    | C <sub>9</sub> H <sub>9</sub> O <sub>3</sub> NS   | 51.19        | 4.30 | 6.63  | 51.01 | 4.10 | 6.39 | 1630                                                          |
| e    | C <sub>13</sub> H <sub>8</sub> O <sub>3</sub> NS  | 60.23        | 3.50 | 5.40  | 60.07 | 3.59 | 5.33 | 1600                                                          |
| f    | C <sub>14</sub> H <sub>11</sub> O <sub>3</sub> NS | 61.54        | 4.06 | 5.13  | 61.43 | 4.15 | 4.93 | 1600                                                          |
| g    | C <sub>9</sub> H <sub>9</sub> O <sub>3</sub> NS   | 50.70        | 5.20 | 6.57  | 50.85 | 5.13 | 6.58 | 1630                                                          |
| h    | C <sub>10</sub> H <sub>11</sub> O <sub>3</sub> NS | 53.33        | 4.92 | 6.22  | 53.83 | 4.64 | 6.03 | 1630                                                          |
| i    | C <sub>7</sub> H <sub>5</sub> O <sub>3</sub> NS   | 45.91        | 2.75 | 7.65  | 45.79 | 2.66 | 7.68 | 1620                                                          |
| j    | C <sub>8</sub> H <sub>7</sub> O <sub>3</sub> NS   | 48.74        | 3.58 | 7.11  | 48.61 | 3.63 | 6.99 | 1620                                                          |
| XIIa | C <sub>13</sub> H <sub>16</sub> O <sub>3</sub> NS | 55.71        | 5.75 | 10.00 | 55.49 | 5.89 | 9.90 | 1620                                                          |
| b    | C <sub>14</sub> H <sub>18</sub> O <sub>3</sub> NS | 57.13        | 6.17 | 9.52  | 57.52 | 6.35 | 9.61 | 1620                                                          |
| c    | C <sub>14</sub> H <sub>12</sub> O <sub>3</sub> NS | 58.33        | 4.20 | 9.72  | 58.37 | 4.18 | 9.56 | 1620                                                          |

which was caused by the -C=N- stretching absorption superimposed on the -C=C- stretching vibrations of the aromatic system. And the band was distinguished from that due to the -C=N- stretching vibration of cyclized -C=N- of structure VIII, which appeared at a higher wave length than that of the former.

Wertheim<sup>3)</sup> reported that mild hydrolysis of VIIIe gave 2-benzoyloxybenzenesulfonamide. Contrary to this report, by the present experiment, the product having same melting point as shown by Wertheim was obtained but it was proved to be N-benzoyl derivative (IVc) by ferric chloride test, infrared spectral comparison and a mixed melting point determination.

The 1,4,3-benzoxathiazine-4,4-dioxides were very sensitive to acid and alkali, being easily hydrolyzed to N-acyl 2-hydroxybenzenesulfonamide and finally to 2-hydroxybenzenesulfonamide. Treatment of VIII with aqueous ammonia or amine gave corresponding amidine (X) instantly. And also when a solution of VIII in ethanol was refluxed for several hours or allowed to stand for several days, the ring opening occurred to afford N-acyl derivative. It is supposed that the carbon atom at the 2-position is considerably electron-poor owing to the influence of the sulfonyl group and easily attacked by the nucleophilic reagents.

2-Substituted amino-1,4,3-benzoxathiazine-4,4-dioxides (XII) were also prepared by the reaction of the corresponding sulfonylurea with phosphorus oxychloride. And the urea was obtained from V *via* the sulfonylurethane, according to the procedure of Marshall, *et al.*<sup>10</sup> as shown in Chart 2.

Infrared spectra of the 1,4,3-benzoxathiazine-4,4-dioxide type such as VIII always exhibited a strong band at approximately  $1620\text{ cm}^{-1}$  which was due to the  $\text{--C=N--}$  stretching vibration and a strong band due to the asymmetric  $\text{SO}_2$  stretching vibration in the vicinity of  $1320\text{ cm}^{-1}$ . And an intense band at approximately  $1180\text{ cm}^{-1}$  was associated with the symmetric  $\text{SO}_2$  stretching vibration. The spectra also possessed with sharp bands in the vicinity of  $1220\text{ cm}^{-1}$  due to the asymmetric  $\text{=CHO--}$  stretching vibrations. The S-N frequency<sup>11</sup> has been tentatively assigned to a strong band at  $1070\text{--}1100\text{ cm}^{-1}$ . In our series also almost all compounds showed a strong absorption band at  $1060\text{--}1090\text{ cm}^{-1}$ .

Concerning 2,3-dihydro-1,4,3-benzoxathiazine-4,4-dioxides, recently Wei, *et al.*<sup>7</sup> reported that simple dihydro derivative could not be obtained. However in our hands, treatment of III with acetaldehyde dimethyl acetal or phenylacetaldehyde in the presence of hydrogen chloride afforded 2-methyl or 2-benzyl-2,3-dihydro-1,4,3-benzoxathiazine-4,4-dioxide (XIIIa,b). They did not reveal instantly a color with alcoholic ferric chloride but on standing for a few minutes brown color appeared and gradually deepened, seemed that ring opening slowly occur with the reagent. The infrared spectrum of XIIIa in KBr-Tablet or in a solution of chloroform showed an absorption band at  $3200\text{ cm}^{-1}$  characteristic for NH group and indicated absence of OH group. Further, the ultraviolet absorption spectra of XIIIa in dioxane, compared with that of IXa, Va, and VIIIi,g supported the cyclic structure and was supported no N-methylene one such as a type of IX as shown in Fig. 1—2. Namely the curve of IXa,

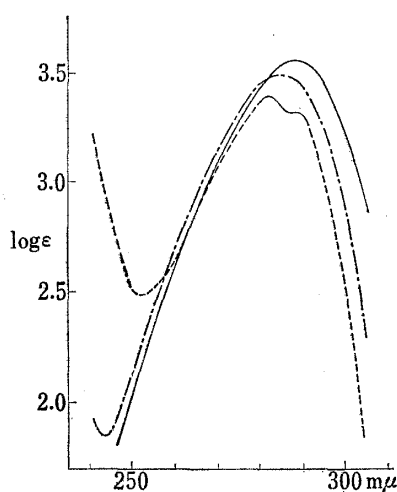


Fig. 1. Ultraviolet Spectral Curves of Va (---), IXa (—), and XIIIa (- - - -) in Dioxane

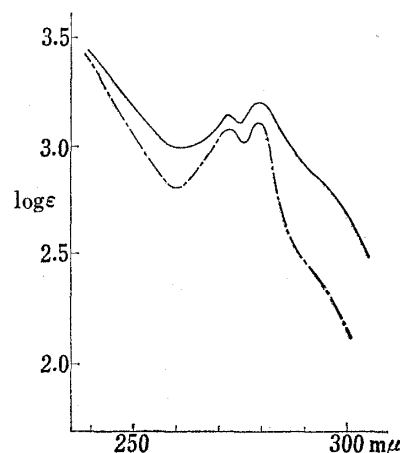


Fig. 2. Ultraviolet Spectral Curves of VIIIi (—) and VIIIg (---) in Dioxane

compared with that of Va, caused a slight bathochromic shift (about  $4\text{ m}\mu$ ) and hyperchromic effect, attributable to the extended conjugation possible when methylene group was jointed to the sulfonamide nitrogen. While the spectrum of XIIIa caused no shift since in all there was present similar conditions for resonance but hypochromic effect and a clearer appearance of fine structure, because of the constrain of the OH group on the molecule enforced by the ring environment and the decrement of the solvent effect. The absorption curves of VIIIi,g, shown in Fig. 2 differed markedly from the absorption of the non-cyclic compounds and of the dihydro

10) F.J. Marshall and M.V. Signal, *J. Org. Chem.*, **23**, 927 (1958).

11) J.N. Baxter, J. Cymerman-Craig, and J.B. Willis, *J. Chem. Soc.*, **1955**, 671.

compounds. This very low intensity and hypsochromic shift of absorption was associated with peculiar arrangement of the unsaturated linkings and unshared electron pair in the benzoxathiazine ring.

Pharmacological studies will be reported at a later date.

### Experimental

Analytical data of IV, VI, and VII are listed in Table I and that of VIII in Table II. Infrared spectra were taken on a Nihon Bunkō Model IR-S. All melting points were uncorrected.

**N-Acetyl-2-hydroxybenzenesulfonamide (IVa)**—To about 200 ml of liq.  $\text{NH}_3$ , set in a dry ice-acetone bath, was added gradually 56 g of 2-acetoxyphenylsulfonyl chloride (Ia),<sup>6</sup> this required one-half hr. The mixture was stirred for an hr after addition was complete. The bath was removed and the mixture was allowed to stand at room temperature overnight. The remainder of the ammonia was removed completely on a hot water bath under reduced pressure. To the resulting crystalline residue was added 250 ml of water and the solution was acidified to congealed paper by the addition of conc. aq. HCl. The acidified mixture was cooled in an ice-box and the crystalline which separated was collected by filtration. Recrystallization from  $\text{H}_2\text{O}$  gave colorless needles, mp 167–170°, weighing 44 g (82.7%). They revealed a purple-brown color with ethanolic  $\text{FeCl}_3$ .

**N-Acetyl-2-hydroxy-5-methylbenzenesulfonamide (IVb)**—a) This was obtained in the same way as described above for IVa from 2-acetoxy-5-methylphenylsulfonyl chloride (Ib)<sup>6</sup> and recrystallized from  $\text{H}_2\text{O}$ -EtOH as colorless needles, mp 196–198°. Yield, 89.4%.

b) VIa (1.0 g) was dissolved in 2.8% aq.  $\text{NH}_3$  (30 ml). After standing for 30 min at room temperature, the solution was acidified with conc. aq. HCl to deposit the product which was recrystallized from  $\text{H}_2\text{O}$ , weighing 0.6 g, mp 196–198°.

**2-Hydroxybenzenesulfonamide (Va)**—A suspension of 31.2 g of IVa and 100 ml of 15% aq. HCl was refluxed, and after the suspension became clear the refluxing was continued for additional 30 min. The mixture, treating with active carbon, was filtered and cooled to deposit 19.8 g of colorless needles, mp 137–141°. After concentrating the filtrate, additional 5.5 g of the same product was obtained. Analytical sample was obtained by the recrystallization from  $\text{H}_2\text{O}$ , mp 140–141° (lit.,<sup>5</sup> mp 139–141°). *Anal.* Calcd. for  $\text{C}_6\text{H}_7\text{O}_3\text{NS}$ : N, 8.09. Found: N, 8.15.

**2-Hydroxy-5-methylbenzenesulfonamide (Vb)**—By the same procedure described for Va, 17.5 g of Vb was obtained from 23.0 g of IVb. It was recrystallized from  $\text{H}_2\text{O}$  as colorless needles, mp 151–152°. *Anal.* Calcd. for  $\text{C}_7\text{H}_9\text{O}_3\text{NS}$ : N, 7.28. Found: N, 7.28.

**N-Acetyl 2-Acetoxy-5-methylbenzenesulfonamide (VIa)**—A mixture of 1.8 g of Vb and 5 ml of  $\text{Ac}_2\text{O}$  was refluxed for 5 hr. The excess  $\text{Ac}_2\text{O}$  was evaporated under reduced pressure to deposit the crystalline residue which was recrystallized from 4 ml of EtOH to give 1.9 g of colorless needles, mp 161°. Ferric chloride test to the product was negative.

**N-Benzoyl 2-Benzoyloxy-5-methylbenzenesulfonamide (VIb)**—In the same manner described for VIIb (described later) except that excess amounts of  $\text{BzCl}$  than twice moles were used, VIb was obtained and recrystallized from iso-PrOH to give colorless needles, mp 119–122°. Yield, 57.6%.

**2-Benzoyloxybenzenesulfonamide (VIIa)**—A mixture of 1.7 g of Va and 1.4 g of  $\text{BzCl}$  was heated at 150° until an evolution of HCl had ceased; It took 15 min. Then the resulting oil was recrystallized from AcOH- $\text{H}_2\text{O}$  to give colorless needles, weighing 2.1 g, mp 172°.

**2-Benzoyloxy-5-methylbenzenesulfonamide (VIIb)**—By the same procedure described above it was obtained from Vb in 76% yield and recrystallized from EtOH to colorless needles, mp 146–147°.

**N-Benzoyl-2-hydroxybenzenesulfonamide (IVc) and 5-Methyl-IVc (IVd)**—When 50 ml of 2.8% aq.  $\text{NH}_3$  was added to 2 g of VIIa or VIIb, the solid was dissolved gradually and a clear solution was obtained. By acidification with dil. aq. HCl, colorless crystals were obtained and recrystallized from EtOH to give colorless needles; IVc, mp 172°, 1.1 g; IVd, mp 204°, 1.0 g.

**2-Benzyl-1,4,3-benzothiadiazine-4,4-dioxide (VIIIa) and 6-Methyl-VIIIa (VIIIb)**—A mixture of 0.02 mole of Va (or Vb) and 4.6 g of phenacylchloride was heated at 150° for 1 hr and cooled. The product was recrystallized from a solvent shown in Table II.

**2-Methyl-1,4,3-benzoxathiazine-4,4-dioxide (VIIIc) and 6-Methyl-VIIIc (VIIId)**—A mixture of 0.01 mole of IVa (or IVb) and 23 ml of xylene with 0.44 g of  $\text{PCl}_3$  (0.51 g of  $\text{POCl}_3$  or 1.4 g of  $\text{P}_2\text{O}_5$ ) was refluxed. The solution became soon clear and HCl evolved. After refluxing for 1.5 hr the reaction mixture was cooled to separate colorless needles which were filtered, washed with EtOH, and recrystallized from a solvent shown in Table II.

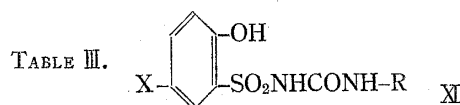
**2-Phenyl-1,4,3-benzoxathiazine-4,4-dioxide (VIIIe) and 6-methyl-VIIIe (VIIIf)**—A mixture of 0.01 mole of Va (or Vb) and 5.4 g of methyl orthobenzoate was heated in an oil bath to 145°. After 30 min the mixture was evaporated *in vacuo* to leave a product which was recrystallized from a solvent shown in Table II.

**2-Ethyl-1,4,3-benzoxathiazine-4,4-dioxide (VIIIg) and 6-Methyl-VIIIg (VIIIh)**—A mixture of 0.01 mole of Va (or Vb) and 5.1 g of ethyl orthopropionate was refluxed for 1.5 hr and the excess propionate was distilled off *in vacuo* to yield crystalline residue which was recrystallized from a solvent shown in Table II.

**N-Ethoxymethylene-2-hydroxybenzenesulfonamide (IXa) and 5-Methyl-IXa (IXb)**—A mixture of 0.01 mole of Va (or Vb) and 7.5 g of ethyl orthoformate was refluxed for 3 hr. The reaction mixture was evaporated to dryness *in vacuo* to afford a viscous oil. Benzene (20 ml) was added to the oil and evaporated to dryness *in vacuo* to give a colorless solid. Recrystallization from *n*-Bu<sub>2</sub>O gave colorless rods. They showed a brown color with alc. FeCl<sub>3</sub>. IXa: Yield, 2.2 g, mp 83°. *Anal.* Calcd. for C<sub>9</sub>H<sub>11</sub>O<sub>4</sub>NS: C, 47.16; H, 4.84; N, 6.11. Found: C, 47.54; H, 4.81; N, 6.19. IXb: Yield, 2.2 g, mp 114–116°. *Anal.* Calcd. for C<sub>10</sub>H<sub>13</sub>O<sub>4</sub>NS: C, 49.38; H, 5.39; N, 5.76. Found: C, 49.27; H, 5.38; N, 5.68.

**1,4,3-Benzoxathiazine-4,4-dioxide (VIIIi) and 6-Methyl-VIIIi (VIIIj)**—A mixture of 0.01 mole of IXa (or IXb) and 1 ml of POCl<sub>3</sub> in 10 ml of xylene was refluxed for 15 min and cooled. A colorless crystal which separated was collected and recrystallized from a solvent shown in Table II.

**1-[2-Hydroxy-(5-methyl or none)phenylsulfonyl]-3-cyclohexyl(or phenyl)urea (XI)**—To a solution of 0.01 mole of V in 10 ml of 1 N NaOH and 20 ml of Me<sub>2</sub>CO, cooled to 0–5°, was added dropwise 1.1 g of ClCOOEt with stirring and then more 1 N NaOH to keep the reaction alkali. After stirring for 1 hr at 5–10°, 50 ml of H<sub>2</sub>O was added and the solution was acidified to congo red paper with dil. aq. HCl to separate oil which was extracted with CHCl<sub>3</sub>. The extract was washed with H<sub>2</sub>O, dried and evaporated to dryness to yield oily product, revealed brown color with FeCl<sub>3</sub>. To a solution of this product in 10 ml of benzene was added 0.01 mole of the appropriate amine and the clear solution was evaporated to dryness. The residue was heated at 140–150° *in vacuo* for 1 hr to give glass like yellow product which was dissolved in dil. aq. NH<sub>3</sub>. The insoluble material was filtered off and the filtrate was acidified with conc. aq. HCl to yield a crystalline solid which was recrystallized from the solvent shown in Table III. The products are summarized in Table III.

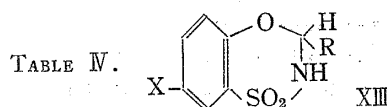


| No. | X               | R         | mp<br>(°C) | Formula                                                         | Analysis (%) |      |      |       |      |      | Yield <sup>a)</sup><br>(%) |
|-----|-----------------|-----------|------------|-----------------------------------------------------------------|--------------|------|------|-------|------|------|----------------------------|
|     |                 |           |            |                                                                 | Calcd.       |      |      | Found |      |      |                            |
|     |                 |           |            |                                                                 | C            | H    | N    | C     | H    | N    |                            |
| XIa | H               | cyclo-hex | 174—175    | C <sub>13</sub> H <sub>18</sub> O <sub>4</sub> N <sub>2</sub> S | 52.34        | 6.08 | 9.39 | 52.58 | 6.24 | 9.29 | 67 <sup>b)</sup>           |
| b   | CH <sub>3</sub> | cyclo-hex | 189—194    | C <sub>14</sub> H <sub>20</sub> O <sub>4</sub> N <sub>2</sub> S | 53.84        | 6.45 | 8.97 | 53.99 | 6.66 | 8.82 | 61 <sup>b)</sup>           |
| c   | CH <sub>3</sub> | Ph        | 221—224    | C <sub>14</sub> H <sub>14</sub> O <sub>4</sub> N <sub>2</sub> S | 54.90        | 4.61 | 9.15 | 55.13 | 4.83 | 9.01 | 55 <sup>c)</sup>           |

a) All products are colorless needles.

b) Recrystallized from MeCN.

c) Recrystallized from EtOH+H<sub>2</sub>O.



| No.   | X               | R                  | mp<br>(°C) | Formula                                           | Analysis (%) |      |      |       |      |      | Yield <sup>a)</sup><br>(%) |
|-------|-----------------|--------------------|------------|---------------------------------------------------|--------------|------|------|-------|------|------|----------------------------|
|       |                 |                    |            |                                                   | Calcd.       |      |      | Found |      |      |                            |
|       |                 |                    |            |                                                   | C            | H    | N    | C     | H    | N    |                            |
| XIIIa | H               | CH <sub>3</sub>    | 139—141    | C <sub>8</sub> H <sub>9</sub> O <sub>3</sub> NS   | 48.24        | 4.56 | 7.03 | 48.31 | 4.58 | 7.04 | 89 <sup>b)</sup>           |
| b     | CH <sub>3</sub> | CH <sub>3</sub>    | 164—165    | C <sub>9</sub> H <sub>11</sub> O <sub>3</sub> NS  | 50.70        | 5.20 | 6.75 | 50.75 | 5.38 | 6.85 | 78 <sup>c)</sup>           |
| c     | CH <sub>3</sub> | CH <sub>2</sub> Ph | 150—151    | C <sub>15</sub> H <sub>15</sub> O <sub>3</sub> NS | 62.28        | 5.23 | 4.84 | 62.35 | 5.37 | 4.82 | 42 <sup>d)</sup>           |

a) All products are colorless rods.

b) Prepd. from Va and MeCH(OEt)<sub>2</sub>. Recrystallized from ligroin+EtOH.

c) Prepd. from Vb and MeCH(OEt)<sub>2</sub>. Recrystallized from benzene.

d) Prepd. from Vb and PhCH<sub>2</sub>CHO. Recrystallized from EtOH.

**2-Cyclohexyl(or Phenyl)amino-(6-methyl- or none)-1,4,3-benzoxathiazine-4,4-dioxide (XII)**—A suspension of 3 g of XI and 15 g of  $\text{POCl}_3$  was heated at  $120^\circ$  for 30 min, during the heating HCl gas evolved and the mixture became clear. Excess  $\text{POCl}_3$  was evaporated *in vacuo* to yield crystalline product which was rinsed with cooled  $\text{H}_2\text{O}$  and recrystallized from appropriate solvent. The products are summarized in Table II.

**Hydrolysis of VIIIe to IVc**—When 0.5 g of VIIIe suspended in 2 ml of 1 N NaOH and 2 ml of  $\text{Me}_2\text{CO}$  was warmed on a water bath ( $85^\circ$ ) for a min, clear solution was formed. After cooling and acidifying with dil. aq. HCl the precipitates formed were collected and recrystallized from AcOH to give colorless needles, mp  $176\text{--}177^\circ$ . The material was positive for  $\text{FeCl}_3$  test and identified as IVc on the basis of the mixture melting point and infrared absorption spectra comparison.

**N-2-Hydroxyphenylsulfonylbezamidine (X:  $\text{R}=\text{C}_6\text{H}_5$ ,  $\text{R}'=\text{H}$ )**—A suspension of 0.5 g of VIIIe in 4% aq.  $\text{NH}_3$  and 4 ml of MeOH was warmed on a water bath ( $85^\circ$ ) for 2 min to form clear solution. The solution was cooled, acidified with dil. HCl and allowed to stand overnight in an ice-box. Colorless needles which separated were collected and recrystallized from MeOH to give 0.2 g of colorless long needles, mp  $102\text{--}104^\circ$ . IR  $\lambda_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 3480, 3220 (broad), 1650. *Anal.* Calcd. for  $\text{C}_{13}\text{H}_{12}\text{O}_3\text{N}_2\text{S}$ : C, 56.52; N, 4.38; S, 10.14. Found: C, 56.68; H, 4.45; N, 9.91.

**N,N-Pentamethylene-N'-(2-hydroxyphenylsulfonyl)formamidine (X;  $\text{R}=\text{H}$ ,  $\text{N} \begin{smallmatrix} \text{R}' \\ \text{R} \end{smallmatrix} = \text{N} \langle (\text{CH}_2)_5 \rangle$ )**—VIIIi (1.0 g) was added to 5 ml of 50% aq. piperidine and the mixture was stirred until the crystals had dissolved and then acidified with dil. aq. HCl. Upon cooling in the ice-box overnight, the crystalline product which separated was filtered and recrystallized from EtOH to give colorless needles, mp  $135\text{--}136^\circ$ , weighing 0.2 g. IR  $\lambda_{\text{max}}^{\text{KBr}}$   $\text{cm}^{-1}$ : 3320 (broad) (OH), 1620 ( $-\text{C}=\text{N}-$ ). *Anal.* Calcd. for  $\text{C}_{12}\text{H}_{16}\text{O}_3\text{N}_2\text{S}$ : C, 53.73; H, 6.01; N, 10.44. Found: C, 53.33; H, 5.87; N, 10.45.

**2-R-(6-methyl or none)-2,3-dihydro-1,4,3-benzoxathiazine-4,4-dioxide (XIII)**—A suspension of each 0.01 mole of V and aldehyde or acetal in 12 ml of  $\text{CH}_2\text{Cl}_2$  was saturated with dry HCl under cooling in an ice-water bath. The solution became clear while the saturating and was stirred for 2 hr after removal of the bath and then evaporated under reduced pressure to afford crystalline residue which was recrystallized from a solvent shown in Table IV.

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