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Studies on Hypoglycemic Agents. IV.[1] Synthesis of 1,4,3-Benzoxathiazine-4,4-dioxides

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2–Hydroxybenzenesulfonamides were prepared in good yield from 2–acetoxyphenylsulfonylchlorides *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.

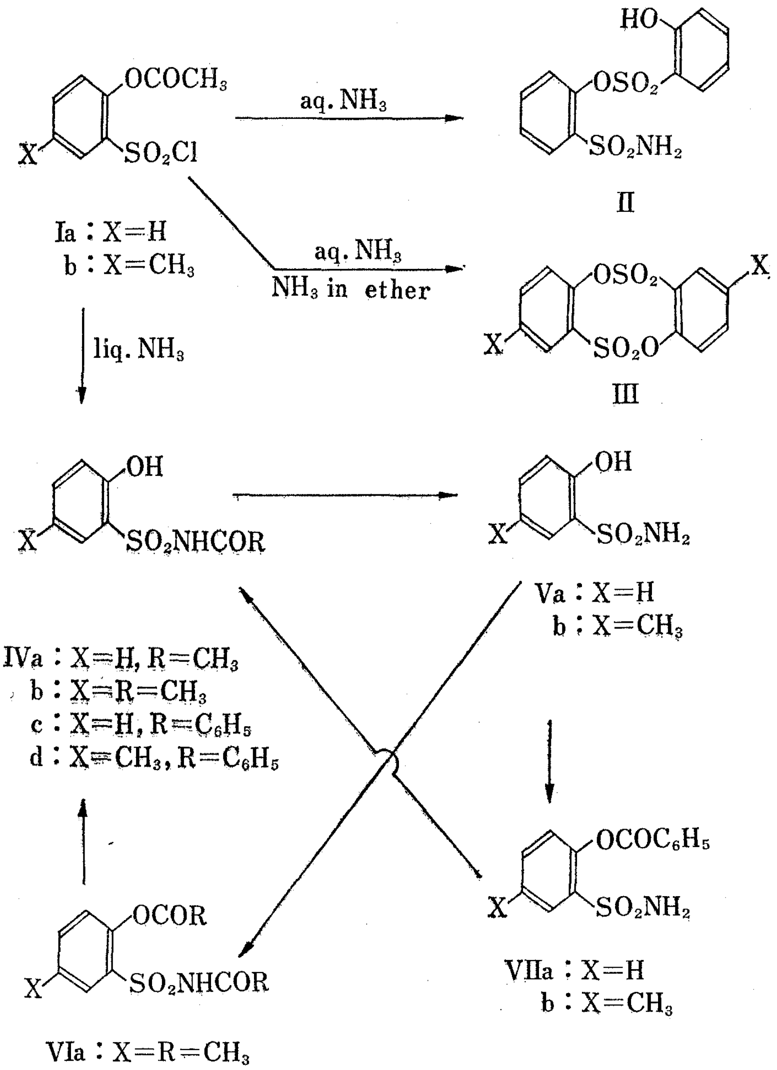


Chart 1

1) Part III: *Yakugasku Zasshi*, **84**, 1024 (1964).
2) Location: *1–3, Ukima, Kita–ku, Tokyo.*

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,[3] in the course of the preparation of diphensaccharin 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[4] obtained V(X=H) by the diazotization of 2-aminobenzenesulfonamide. However Bartram, *et al.*[5] 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 debenzylation. Further, he described that reaction of 2-acetoxyphenylsulfonyl chloride (I, X=H) with aqueous ammonia gave a compound, probably 2-(2-hydroxyphenylsulfonyloxy)benzenesulfonamide (II) as sole product. Anschütz[6] 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.*[7] 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 (%) Calcd. C	H	N	Found C	H	N	IR ν_{max} cm^{-1} in KBr-Tablet –CO–N	–CO–O
IVa	$C_8H_9O_4NS$	44.66	4.22	6.51	44.61	4.08	6.10	1680	—
IVb	$C_9H_{11}O_4NS$	47.16	4.84	6.11	47.25	4.91	5.56	1685	—
IVc	$C_{13}H_{11}O_4NS$	56.32	4.00	5.05	56.59	3.97	4.98	1690	—
IVd	$C_{14}H_{13}O_4NS$	57.73	4.50	4.82	57.75	4.53	4.29	1655	—
VIa	$C_{11}H_{13}O_5NS$	48.71	4.83	5.16	48.71	4.75	4.86	1675	1770
VIb	$C_{21}H_{17}O_5NS$	63.79	4.33	3.54	64.19	4.59	3.42	1690	1730
VIIa	$C_{13}H_{11}O_4NS$	56.32	4.00	5.05	55.92	4.22	4.66	—	1720
VIIb	$C_{14}H_{13}O_4NS$	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**, 8509*a* (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).

The compound (V) was heated with acetic anhydride or acetylchloride under refluxing to afford always O,N–diacetyl derivative (VIa). However by the action of an equimolar amount of benzoyl chloride, V afforded O–benzoyl derivatives (VII), and by the excess, O,N–dibenzoyl derivative (VIb), on heating at the temperature that the evolution of hydrogen chloride began. However, desired cyclized product, 2–benzyl–1,4,3–benzoxathiazine–4,4–dioxide (VIIIa and VIIIb), was obtained by the treatment of V with phenacyl chloride under the same condition described above. Its structural proof was made by infrared absorption spectra and elementary analysis. When VII was treated with dilute aqueous ammonia, O→N rearrangement occurred to afford IVc,d. O,N–Diacyl derivative (VI) also gave the corresponding N–acyl derivative (IV) under the same treatment. These chemical behaviours were similar to those of O–acyl salicylamides.[8,9]

Some attempts to obtain 2–substituted–1,4,3–benzoxathiazine–4,4–dioxide from IV by applying the condition[9] which produced 1,3–benzoxazin–4–one derivatives from N–acyl salicylamide were unsuccessful. But when IVa or IVb was refluxed in xylene containing phosphorus oxychloride, cyclization occurred to afford the desired substance (VIIIc or VIIId). The infrared spectrum of the product showed that the absorption bands at 3200, 3400, and 1680 cm^{-1} attributed to the NH, OH, and C=O groups of IVa had disappeared and that the band at 1630 cm^{-1} characteristic for –C=N– group appeared. And the elemental analysis of the product indicated the empirical formula, corresponding to 2–methyl–1,4,3–benzoxathiazine–4,4–dioxide.

In an analogous fashion, it was failure to prepare 2–phenyl derivative (VIIIe, f) from IVc,d. But the compounds were easily obtained by the reaction of V with methyl orthobenzoate quantitatively. Similarly 2–ethyl derivatives (VIIIg,h) were obtained from V and ethyl orthopropionate. Under the condition affecting ring formation with above orthoester, ethyl orthoformate reacted with V to yield N–ethoxymethylene derivative (IX), which seemed to be the intermediate in the course of the cyclization, and the formation of the VIIIi,j was not observed. The compound (IX) was cyclized to VIIIi,j by treatment with phosphorus oxychloride. Infrared spectra of IX showed the somewhat broad strong bands at 3300 cm^{-1} assigned to OH stretching vibration. In addition a strong band was present at 1590 cm^{-1}

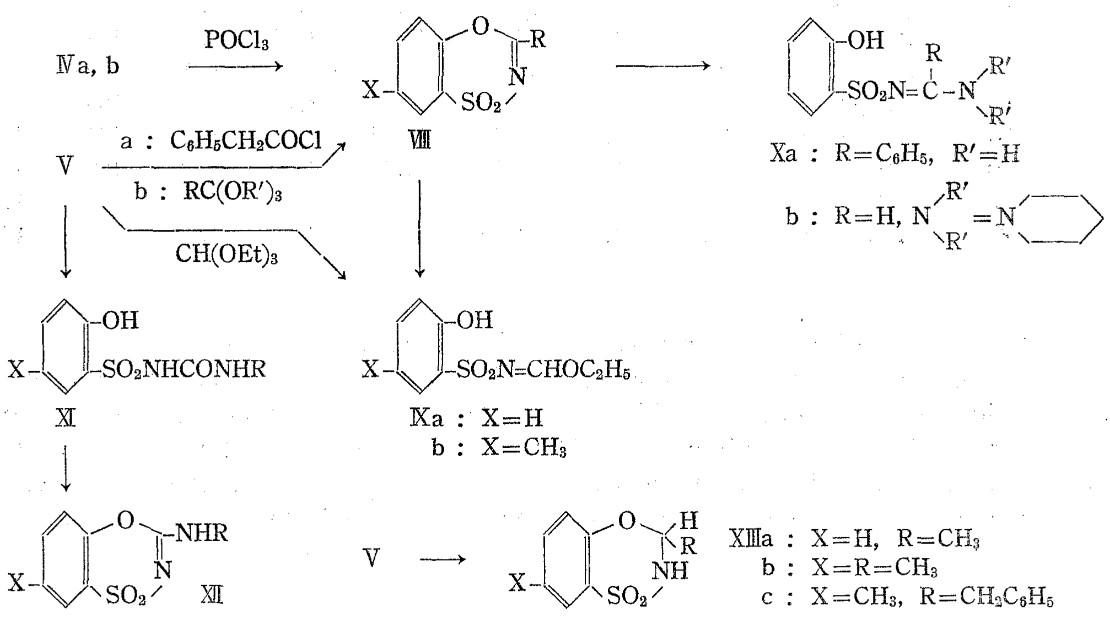
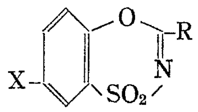


Chart 2

8) A.W. Titherley and W.L. Hicks, *J. Chem. Soc.*, **95**, 908 (1909).
9) T. Hanada, *Bull. Chem. Soc. Japan*, **31**, 1024 (1956).

Table II.  VIII, XII

No.	X	R	mp (°C)	Recryst. solvent	Appearance	Prepd. from	Yield (%)
VIIIa	H	CH_2Ph	157—158	EtOH	plates	Va+$PhCH_2COCl$	62
b	CH_3	CH_2Ph	151—152	EtOH	prisms	Vb+$PhCH_2COCl$	58
c	H	CH_3	179—182	EtOH	needles	IVa	36
d	CH_3	CH_3	183—184	EtOH	long plates	IVb	67
e	H	Ph	176—177	EtOH	neeldes	Va+$PhC(OMe)_3$	92
f	CH_3	Ph	212—214	EtOH	neeldes	Vb+$PhC(OMe)_3$	96
g	H	C_2H_5	117—118	Xylene	long plates	Va+$EtC(OEt)_3$	92
h	CH_3	C_2H_5	154	Benzene	long plates	Vb+$EtC(OEt)_3$	94
i	H	H	161—164	Benzene	needles	IXa	17
j	CH_3	H	166—169	Benzene	long plates	IXb	25
XIIa	H	HN-⟨H⟩	209—212	MeCN	needles	XIa	39
b	CH_3	HN-⟨H⟩	173—176	MeCN	needles	XIb	44
c	CH_3	NHPh	271—272	EtOH	needles	XIc	43

No.	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	IR ν_{max} cm^{-1} in KBr-Tablet -C=N-
VIIIa	$C_{14}H_{11}O_3NS$	61.54	4.06	5.13	61.87	4.38	5.43	1640
b	$C_{15}H_{13}O_3NS$	62.71	4.56	4.88	62.75	4.85	5.04	1630
c	$C_8H_7O_3NS$	48.74	3.58	7.11	49.00	3.58	6.87	1630
d	$C_9H_9O_3NS$	51.19	4.30	6.63	51.01	4.10	6.39	1630
e	$C_{13}H_9O_3NS$	60.23	3.50	5.40	60.07	3.59	5.33	1600
f	$C_{14}H_{11}O_3NS$	61.54	4.06	5.13	61.43	4.15	4.93	1600
g	$C_9H_9O_3NS$	50.70	5.20	6.57	50.85	5.13	6.58	1630
h	$C_{10}H_{11}O_3NS$	53.33	4.92	6.22	53.83	4.64	6.03	1630
i	$C_7H_5O_3NS$	45.91	2.75	7.65	45.79	2.66	7.68	1620
j	$C_8H_7O_3NS$	48.74	3.58	7.11	48.61	3.63	6.99	1620
XIIa	$C_{13}H_{16}O_3NS$	55.71	5.75	10.00	55.49	5.89	9.90	1620
b	$C_{14}H_{18}O_3NS$	57.13	6.17	9.52	57.52	6.35	9.61	1620
c	$C_{14}H_{12}O_3NS$	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[3] 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 comparision 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 finaly 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 oppening 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.*[10] 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 cm^{-1} which was due to the –C=N– stretching vibration and a strong band due to the asymmetric SO_2 stretching vibration in the vicinity of 1320 cm^{-1}. And an intense band at approximately 1180 cm^{-1} was associated with the symmetric SO_2 stretching vibration. The spectra also possessed with sharp bands in the vicinity of 1220 cm^{-1} due to the asymmetric =CHO– stretching vibrations. The S–N frequency[11] has been tentatively assigned to a strong band at 1070—1100 cm^{-1}. In our series also almost all compounds showed a strong absorption band at 1060—1090 cm^{-1}.

Concerning 2,3–dihydro–1,4,3–benzoxathiazine–4,4–dioxides, recently Wei, *et al.*[7] 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 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,

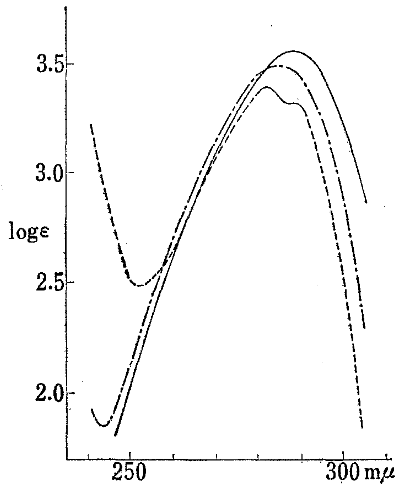


Fig. 1. Ultraviolet Spectral Curves of Va (— - —), IXa (——), and XIIIa (- - - - -) in Dioxane

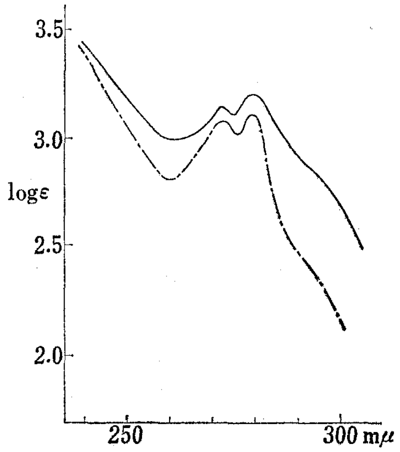


Fig. 2. Ultraviolet Spectral Curves of VIIIi (——) and VIIIg (— - —) in Dioxane

compared with that of Va, caused a slight bathochromic shift (about 4 mμ) 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. NH_3, set in a dry ice–acetone bath, was added gradually 56 g of 2-acetoxyphenylsulfonyl chloride (Ia),[6] 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 congored 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 filteration. Recrystallization from H_2O gave colorless needles, mp 167—170°, weighing 44 g (82.7%). They revealed a purple-brown color with ethanolic $FeCl_3$.

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)[6] and recrystallized from H_2O–EtOH as colorless needles, mp 196—198°. Yield, 89.4%.

b) VIa (1.0 g) was dissolved in 2.8% aq. 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 H_2O, 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 deposite 19.8 g of colorless needles, mp 137—141°. After concentrating the filtrate, additional 5.5 g of the same prdocut was obtained. Analytical sample was obtained by the recrystallization from H_2O, mp 140—141° (lit.,[5] mp 139—141°). *Anal.* Calcd. for $C_6H_7O_3NS$: 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 H_2O as colorless needles, mp 151—152°. *Anal.* Calcd. for $C_7H_9O_3NS$: 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 Ac_2O was refluxed for 5 hr. The excess Ac_2O was evaporated under reduced pressure to deposite 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 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 BzCl was heated at 150° until an evolution of HCl had ceased; It took 15 min. Then the resulting oil was recrystallized from AcOH–H_2O 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. 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 PCl_3 (0.51 g of $POCl_3$ or 1.4 g of P_2O_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.

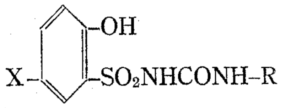
2-Ethyl-1,4,3-benzoxathiazine-4,4-dioxide (VIIIg) and 6-Methyl-VIIIg (VIIIh)——A mixture of 0.01 mole of Va (or Vb) and 5.1 g of ethyl orthopropionate was refluxed for 1.5 hr and the excess propionate was distilled off *in vacuo* to yield crystalline residue which was recrystallized from a solvent shown 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 ortoformate 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_2O gave colorless rods. They showed a brown color with alc. $FeCl_3$. IXa: Yield, 2.2 g, mp 83°. *Anal.* Calcd. for $C_9H_{11}O_4NS$: 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 $C_{10}H_{13}O_4NS$: 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 $POCl_3$ 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_2CO, 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_2O was added and the solution was acidified to congo red paper with dil. aq. HCl to separate oil which was extracted with $CHCl_3$. The extract was washed with H_2O, dried and evaporated to dryness to yield oily product, revealed brown color with $FeCl_3$. 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_3. 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.

TABLE III.

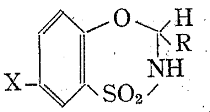


XI

No.	X	R	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	Yield[a)] (%)
XIa	H	cyclo–hex	174—175	$C_{13}H_{18}O_4N_2S$	52.34	6.08	9.39	52.58	6.24	9.29	67[b)]
b	CH_3	cyclo–hex	189—194	$C_{14}H_{20}O_4N_2S$	53.84	6.45	8.97	53.99	6.66	8.82	61[b)]
c	CH_3	Ph	221—224	$C_{14}H_{14}O_4N_2S$	54.90	4.61	9.15	55.13	4.83	9.01	55[c)]

a) All products are colorless needles.
b) Recrystallized from MeCN.
c) Recrystallized from EtOH+H_2O.

TABLE IV.



XIII

No.	X	R	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	Yield[a)] (%)
XIIIa	H	CH_3	139—141	$C_8H_9O_3NS$	48.24	4.56	7.03	48.31	4.58	7.04	89[b)]
b	CH_3	CH_3	164—165	$C_9H_{11}O_3NS$	50.70	5.20	6.75	50.75	5.38	6.85	78[c)]
c	CH_3	CH_2Ph	150—151	$C_{15}H_{15}O_3NS$	62.28	5.23	4.84	62.35	5.37	4.82	42[d)]

a) All products are colorless rods.
b) Prepd. from Va and $MeCH(OEt)_2$. Recrystallized from ligroin+EtOH.
c) Prepd. from Vb and $MeCH(OEt)_2$. Recrystallized from benzene.
d) Prepd. from Vb and $PhCH_2CHO$. 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 $POCl_3$ was heated at 120° for 30 min, during the heating HCl gas evolved and the mixture became clear. Excess $POCl_3$ was evaporated *in vacuo* to yield crystalline product which was rinsed with cooled H_2O 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 Me_2CO was warmed on a water bath (85°) for a min, clear solution was formed. After cooling and acidifing with dil. aq. HCl the precipitates formed were collected and recrystallized from AcOH to give colorless needles, mp 176—177°. The material was positive for $FeCl_3$ test and identified as IVc on the basis of the mixture melting point and infrared absorption spectra comparison.

N-2-Hydroxyphenylsulfonylbezamidine (X: R=C_6H_5, R′=H)——A suspension of 0.5 g of VIIIe in 4% aq. NH_3 and 4 ml of MeOH was warmed on a water bath (85°) 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—104°. IR λ_{max}^{KBr} cm^{-1}: 3480, 3220 (broad), 1650. *Anal.* Calcd. for $C_{13}H_{12}O_3N_2S$: C, 56.52; N, 4.38; N, 10.14. Found: C, 56.68; H, 4.45; N, 9.91.

N,N-Pentamethylene-N′-(2-hydroxyphenylsulfonyl)formamidine (X; R=H, $N\langle^{R'}_{R'}$=$N\langle(CH_2)_5$)——VIIIi (1.0 g) was added to 5 ml of 50% aq. piperidine and the mixture was stirred unitl 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—136°, weighing 0.2 g. IR λ_{max}^{KBr} cm^{-1}: 3320 (broad) (OH), 1620 (–C=N–). *Anal.* Calcd. for $C_{12}H_{16}O_3N_2S$: 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 CH_2Cl_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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