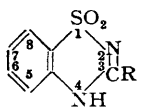
356. *Derivatives of Benz*-1 : 2 : 4-*thiadiazine* 1 : 1-*Dioxide.*

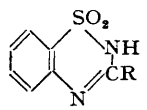
By D. V. Parke and R. T. Williams.

Orthanilamide and substituted orthanilamides when heated with urea at 180° give rise to 3-keto-3 : 4-dihydrobenz-1 : 2 : 4-thiadiazine 1 : 1-dioxide and its derivatives. It has been shown that in this reaction cyanic acid, formed by the decomposition of urea, combines with the orthanilamide to give a substituted urea which then cyclizes with loss of ammonia to form a benzthiadiazine. A number of benzthiadiazine 1 : 1-dioxide derivatives has been made by heating orthanilamides with formic acid at 100°. Observations on the spectra of these compounds have also been made.

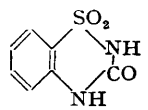
Our interest in the chemistry of the benzthiadiazine system was aroused when one of us (Williams, *Biochem. J.*, 1945, **39,** xi), suspected that a crystalline compound (Found: C, 48·5; H, 5·3; N, 14·2; S, 16·0. Calc. for $C_8H_8O_2N_2S$: C, 48·95; H, 4·1; N, 14·3; S, 16·3%) which he had isolated in small amounts from the urine of rabbits dosed with orthanilamide (*o*-aminobenzenesulphonamide) was 3-methylbenz-1 : 4 : 2-thiadiazine 1 : 1-dioxide (I; R = Me) [this compound can also be formulated as a 1 : 2 : 4-thiadiazine (I*a*)]. It was suspected that this



(I.)



(I*a*.)



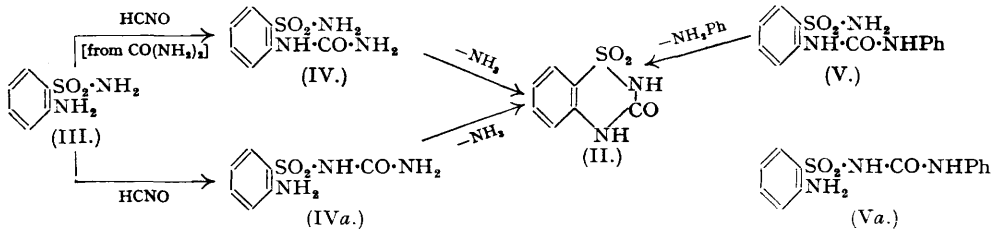
(II.)

compound had arisen by dehydration of acetylorthanilamide, a metabolite of orthanilamide. Only four compounds of this heterocyclic series had been recorded in the literature, namely, benz-1 : 2 : 4-thiadiazine 1 : 1-dioxide itself (I; R = H) and its 3-methyl and 3 : 4-dimethyl derivatives [Ekbom, *Bihang, K. Svenska Vet.-Akad. Handl.*, 1902, **27** (II), 3], and 3-keto-3 : 4-dihydrobenz-1 : 2 : 4-thiazine 1 : 1-dioxide (II) (Schräder, *J. pr. Chem.*, 1917, **95**, 392). It seemed of interest, therefore, to study further the chemistry of this type of compound.

The 3-keto-derivative (II) has a saccharin-like taste and was prepared by Schräder (*loc. cit.*) from saccharin by way of *o*-sulphonamidobenzoylazide during a Curtius rearrangement. We have found that it can very easily be prepared in excellent yield by heating orthanilamide with urea at about 180° Substituted orthanilamides react similarly and we have prepared the 6-nitro-, 7-bromo-, and 5-hydroxy-derivatives of (II) from 4-nitro-, 5-bromo-, and 3-hydroxy-orthanilamide, respectively. 7-Nitro-3-keto-3 : 4-dihydrobenz-1 : 2 : 4-thiadiazine 1 : 1-dioxide was readily obtained by nitration of (II).

At the temperature of the reaction urea dissociates to ammonia and cyanic acid and therefore

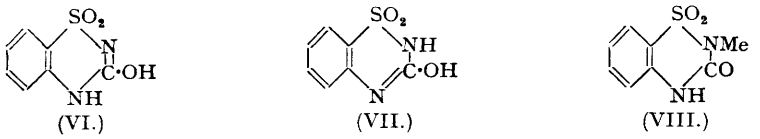
it appears likely that orthanilamide (III) actually combines with cyanic acid to give a substituted urea (IV or IV*a*), which could then lose ammonia to give (II). The possibility of the formation



of (IV*a*) in such a melt reaction has to be considered because, for example, White, Bratton, Litchfield, and Marshall (*J. Pharmacol.*, 1941, **72**, 112) have shown that, when sulphanilamide is fused with dicyanodiamide, the sulphonamide group is attacked and the product is mainly sulphanilylguanidine.

Support for this type of mechanism was obtained. *N*-Phenyl-*N'*-(*o*-sulphamylphenyl)urea (V) was prepared from orthanilamide and phenyl *iso*cyanate at 100°. When carefully heated, this decomposed to aniline and (II). When orthanilamide and phenyl *iso*cyanate are heated together, the formation of (V*a*) is possible; however, the product of the reaction appears to be (V), because it gave negative tests for an aromatic primary amino-group and was readily soluble in alkali but not in acid.

Two other possible structures (VI and VII) can be written for (II). We have been able to show, however, that the compound has the lactam structure (II). On methylation the lactim



structures (VI or VII) should yield a 3-methoxy-derivative (I or I*a*; R = OMe) whereas the lactam structure should yield a *N*-methyl derivative, probably (VIII). With methyl sulphate and alkali, the compound yielded a monomethyl derivative which contained no methoxyl group (Zeisel method) and is probably 3-keto-2-methyl-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide (VIII). The ultra-violet absorption spectrum of this compound was very similar to that of (II) and quite different from that which would be expected for the lactim structure (VI or VII).

Compounds with the lactim structure (I or I*a*; R = H) were readily obtained by heating orthanilamide or its substituted derivatives with formic acid at 100° (cf. Ekbom, *loc. cit.*). 5-Hydroxy-, 7-bromo-, and 6-nitro-benzthiadiazine 1 : 1-dioxide were prepared from 3-hydroxy-, 5-bromo-, and 4-nitro-orthanilamide respectively. The 3-methyl derivative (I or I*a*; R = Me) was prepared by heating diacetylorthanilamide—it was originally prepared by Ekbom (*loc. cit.*) by heating monoacetylorthanilamide, but we were unable to prepare the monoacetyl derivative by heating orthanilamide on the water-bath with acetic anhydride according to his directions. We found that acetic anhydride and orthanilamide gave mainly diacetylorthanilamide. By use of equal volumes of acetic acid and acetic anhydride a mixture of acetyl derivatives was obtained, from which monoacetylorthanilamide could only be obtained with difficulty and in small yield. Monoacetylorthanilamide was readily transformed into 3-methylbenzthiadiazine 1 : 1-dioxide, even on recrystallization from hot water. Acetylation of orthanilamide with pyridine and acetic anhydride yielded diacetylorthanilamide almost quantitatively.

Since 3-keto-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide has a very sweet taste, the tastes of its derivatives are recorded in the Table I. Benzthiadiazine 1 : 1-dioxide derivatives not containing a keto-group were either tasteless or slightly bitter.

In the region 200—400 mμ. the ketodihydrothiadiazine 1 : 1-dioxides (II) in ethanol showed three absorption bands which appeared to correspond to those of the parent orthanilamide (III). The formation of the second ring with the introduction of a keto-group had little effect on the position of the maxima (see Table II), except for that of longest wave-length which is shifted in all cases to a shorter wave-length. The spectra of the benzthiadiazine 1 : 1-dioxides (I or I*a*) in ethanol, however, were different from those of the keto-dihydro-derivatives (II). In general, the former showed two absorptions bands (Table III) instead of the three shown by the

keto-derivatives, in consequence, no doubt, of the introduction of a double bond into the heterocyclic ring.

TABLE I.

3-Keto-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide	very sweet	7-Bromo-derivative	almost tasteless (faintly acid)
7-Nitro-derivative	intensely bitter	5-Hydroxy- ,,	tasteless
6-Nitro- ,,	slightly bitter	2-Methyl ,,	,,

TABLE II.

	$\lambda_{max.}$, mμ.	ε × 10^{-3}.	$\lambda_{max.}$, mμ.	ε × 10^{-3}.	$\lambda_{max.}$, mμ.	ε × 10^{-3}.
Orthanilamide	206	26·0	245—246	8·6	308	3·5
3-Keto-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide	204 206	29·0 28·0	245	10·8	289	1·7
			(243	10·9	290	2·0) *
3-Keto-2-methyl-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide	208 210	26·0 24·5	249	12·6	290	2·1
5-Bromo-orthanilamide	206	24·0	253	12·0	324	3·2
7-Bromo-3-keto-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide	206	24·6	256	14·5	305	1·7
4-Nitro-orthanilamide	—	—	238	18·9	382	2·2
6-Nitro-3-keto-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide	—	—	240 ~280	22·7 4·5	345	1·8
3-Hydroxyorthanilamide	210 224	24·6 23·0	~252	5·2	325	5·2
5-Hydroxy-3-keto-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide	210 (218	36·4 24·4	247 260	6·8 7·6	298 314	3·4 5·6) *
7-Nitro-3-keto-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide	205	17·2	~242	5·2	325 329	12·5 12·5

* In 0·1N-NaOH.

TABLE III.

Compound.*	$\lambda_{max.}$, mμ.	ε × 10^{-3}.	$\lambda_{max.}$, mμ.	ε × 10^{-3}.	$\lambda_{max.}$, mμ.	ε × 10^{-3}.
Benzthiadiazine 1 : 1-dioxide	207	13·4	269	7·6	—	—
3-Methyl derivative	214	8·8	266	7·9	—	—
7-Bromo- ,,	215	10·9	291	13·1	—	—
6-Nitro- ,,	216	6·2	261 266	15·6 16·1	~292 368	10·4 1·35

* In ethanol.

EXPERIMENTAL.

Absorption spectra were determined with a Unicam Quartz Spectrophotometer, Model S.P. 500. M. p.s are uncorrected.

3-Keto-3 : 4-dihydrobenz-1 : 2 : 4-thiadiazine 1 : 1-Dioxide Derivatives.—*3-Keto-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide.* Orthanilamide (10 g.) and urea (7 g.) were intimately mixed and heated to 180°. Ammonia was evolved and after 30 minutes the mixture suddenly crystallized. The product was cooled and dissolved in hot water (100 c.c.), treated with charcoal, and filtered. On acidification of the solution with dilute hydrochloric acid, the compound crystallized. After an hour at 0°, the white crystals were filtered off, washed with water, and dried (10·4 g., 94%). The compound (colourless needles) was purified by recrystallization from water containing a little ethanol. It had a very sweet saccharin-like taste and m. p. 305° (Schräder, *loc. cit.*, gives m. p. 287—288°) (Found: C, 42·8; H, 3·1; N, 14·1. Calc. for $C_7H_6O_3N_2S$: C, 42·4; H, 3·0; N, 14·1%). The substance was acidic and dissolved in sodium carbonate solution with effervescence.

On methylation with methyl sulphate and alkali, it gave *3-keto-2-methyl-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide* in poor yield as white needles, m. p. 238—240°, from aqueous ethanol (Found: C, 45·0; H, 3·3; N, 12·9; OMe, 0. $C_8H_8O_3N_2S$ requires C, 45·3; H, 3·8; N, 13·2; OMe, 0%).

7-Nitro-3-keto-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide. The 3-keto-derivative (10 g.) was dissolved in concentrated sulphuric acid (10 c.c.) and nitrated at 0—5° with a mixture of concentrated nitric (3·5 c.c.) and sulphuric acids (4 c.c.). The product was poured on ice and the solid which separated was filtered off and washed with ice-water. On recrystallization from hot water, the *nitro*-compound was obtained as pale buff-coloured plates, m. p. 283° (9 g.) (Found: N, 17·1; S, 12·9. $C_7H_5O_5N_3S$ requires N, 17·3; S, 13·2%). With 10% aqueous sodium hydroxide it formed a deep-orange *sodium* salt, insoluble in strong alkaline solution (Found: Na, 8·8. $C_7H_4O_5N_3SNa$ requires Na, 8·7%). When heated, the salt

became red, and when it was kept for a few hours in the cold the orange colour returned. When kept for a few months the salt became nearly white.

6-*Nitro*-3-*keto*-3 : 4-*dihydrobenzthiadiazine* 1 : 1-*dioxide*. 4-Nitro-2-aminobenzenesulphonamide (0·8 g.) (Thorpe and Williams, *Biochem. J.*, 1941, **35**, 61) and urea (0·7 g.) were intimately mixed and heated at 200°. Ammonia was evolved and after 15 minutes the melt crystallized. The product was dissolved in hot water; the solution was treated with charcoal and filtered. On cooling the 6-*nitro*-compound crystallized as yellow prisms, m. p. 270° (0·7 g.) (Found : C, 34·7; H, 2·0; N, 16·9; S, 12·5. $C_7H_5O_5N_3S$ requires C, 34·6; H, 2·1; N, 17·3; S, 13·2%). This compound also formed an orange sodium salt which became red when heated.

7-*Bromo*-3-*keto*-3 : 4-*dihydrobenzthiadiazine* 1 : 1-*dioxide*. Bromo-orthanilamide (0·5 g.) (Parke and Williams, preceding paper) and urea (0·5 g.) were heated to 150°, ammonia being evolved. The temperature was allowed to rise to 200° and after 10 minutes the melt crystallized. The product was dissolved in hot water and the solution treated with charcoal and filtered. Acidification of the filtrate with hydrochloric acid gave the 7-*bromo*-compound (0·45 g.) as needles. Recrystallized from aqueous ethanol, it had m. p. 335° (Found : N, 10·1; Br, 29·4. $C_7H_5O_3N_3SBr$ requires N, 10·1; Br, 28·8%).

5-*Hydroxy*-3-*keto*-3 : 4-*dihydrobenzthiadiazine* 1 : 1-*dioxide*. 2-Amino-3-hydroxybenzenesulphonamide (229 mg.) intimately mixed with urea (150 mg.) was heated at 180° for 1 hour. The product was boiled with water (charcoal) and filtered. On acidification, the filtrate yielded the 5-*hydroxy*-compound (160 mg., 61%) as white needles, m. p. 275°. It gave a deep-blue colour with ferric chloride, was sparingly soluble in cold water, and titrated as a monobasic acid (Found : C, 39·7; H, 2·9; N, 12·7; S, 15·0; equiv., 219. $C_7H_6O_4N_2S$ requires C, 39·25; H, 2·8; N, 13·1; S, 15·0%; equiv., 214). Acetylation with acetic anhydride gave the 5-*acetyl* derivative as short colourless needles, m. p. 262°, after recrystallization from water (Found : CH_3·CO, 17·0. $C_9H_8O_5N_2S$ requires CH_3·CO, 16·8%).

N-*Phenyl*-N′-(o-*sulphamylphenyl*)*urea*.—Equal weights of orthanilamide (2 g.) and phenyl *iso*cyanate were heated together at 100°. The mixture became pasty and then solidified. After an hour, the solid was dissolved in hot ethanol (charcoal) and filtered, and crystallization induced by dilution with water (yield, 2 g.). The substituted *urea* was recrystallized from aqueous ethanol and formed soft matted needles, m. p. 180° (Found : C, 54·1; H, 4·7; N, 14·1. $C_{13}H_{13}O_3N_3S$ requires C, 53·6; H, 4·5; N, 14·4%). This substance gave no colour when diazotized and coupled with alcoholic dimethyl-α-naphthylamine. It readily dissolved in dilute aqueous sodium hydroxide, but was sparingly soluble in dilute hydrochloric acid.

Action of Heat on N-*Phenyl*-N′-(o-*sulphamylphenyl*)*urea*.—The foregoing compound (0·5 g.) was heated at 220° for an hour in a test-tube with a side-arm. Aniline distilled off (identity proved by colour reactions) and was collected in 5 c.c. of 10% sulphuric acid. The solution of aniline sulphate was made alkaline and extracted with ether. The ether was removed and the residual aniline converted into acetanilide (22 mg.), m. p. 112° not depressed by admixture with authentic acetanilide, m. p. 115°. The residue in the test-tube was dissolved in boiling water, treated with charcoal, and filtered. On acidification with hydrochloric acid and cooling, 280 mg. of pink needles, m. p. 295°, were obtained. These, on recrystallization from water (charcoal), formed colourless needles which were identified by absorption spectra and mixed melting point as 3-keto-3 : 4-dihydrobenzthiadiazine 1 : 1-dioxide.

Benz-1 : 4 : 2-*thiadiazine* 1 : 1-*Dioxide Derivatives*.—These compounds were prepared by heating the appropriate orthanilamide derivative with an equal weight of anhydrous formic acid for an hour on the water-bath. The product was poured into water and the crystals filtered off.

The following were prepared : 6-*Nitrobenzthiadiazine* 1 : 1-*dioxide*, obtained in quantitative yield from 4-nitro-2-aminobenzenesulphonamide (0·12 g.) and formic acid (0·2 c.c.), formed six-sided yellow plates, m. p. 358° (decomp.), which were very sparingly soluble in water (Found : C, 35·7; H, 2·5; N, 17·8. $C_7H_5O_4N_3S,0{\cdot}5H_2O$ requires C, 35·6; H, 2·6; N, 17·8%). Its colour was not intensified on addition of 2N-sodium hydroxide. The 7-*bromo*-compound (from 5-bromo-orthanilamide) formed plates, m. p. 285°, from ethanol (Found : C, 32·8; H, 1·9; N, 10·1; Br, 28·5. $C_7H_5O_2N_3SBr$ requires C, 32·2; H, 1·9; N, 10·7; Br, 30·6%). The 5-*hydroxy*-compound (from 3-hydroxyorthanilamide) formed light-brown prisms, m. p. 263°, from water (Found : C, 42·6; H, 3·2; N, 14·05; S, 16·3. $C_7H_6O_3N_2S$ requires C, 42·4; H, 3·05; N, 14·1; S, 16·2%). It gave a blue colour with ferric chloride. Benzthiadiazine 1 : 1-dioxide, m. p. 222°, was prepared according to Ekbom's directions (*loc. cit.*; he gives m. p. 219—220°) from orthanilamide and formic acid.

3-*Methylbenzthiadiazine* 1 : 1-*Dioxide*. *Acetylation of Orthanilamide*.—Orthanilamide (5 g.) was added to a mixture of pyridine (5 c.c.) and acetic anhydride (10 c.c.). The amide dissolved in 5 minutes and the mixture became warm. Next morning, the *o*-diacetylaminobenzenesulphonamide was filtered off, washed with water (yield, 4·8 g.), and recrystallized from hot water; it formed prisms, m. p. 190° (Found : C, 47·3; 4·9; N, 10·6. Calc. for $C_{10}H_{12}O_4N_2S$: C, 46·9; H, 4·7; N, 10·9%); Ekbom (*loc. cit.*) gives m. p. 191·5—192·5°. When heated for 2 hours at 200° it yielded 3-methylbenzthiadiazine 1 : 1-dioxide, m. p. 269° (Ekbom gives m. p. 263—264°).

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